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ARTHRITIS IN THE MEDITERRANEAN THEATER OF OPERATIONS*

I. Incidence of Joint Disease — Clinical Description of Rheumatoid Arthritis

LIEUTENANT COLONEL CHARLES L. SHORT, M.C., A.U.S.

LIKE other organs of the body, the joints are subject to many different forms of disease and injury of both known and unknown etiology. Since this paper deals chiefly with the medical aspects of joint disorders, strictly surgical conditions, such as the immediate effects of trauma and articular infection associated with wounds, have been excluded. Diseases and injuries of the bones, muscles, tendons, bursas and other supporting structures were not studied unless there was subjective or objective evidence pointing toward joint involvement. The conditions variously labeled arthralgia, myositis, myalgia and fibrositis, although not strictly forms of arthritis, were included, since they are often confused with actual joint disease clinically and are usually put under the heading of arthritis in military medical statistics; furthermore, these diagnoses were frequently encountered in the case records in the Theater and bore a high rate of disability. Again, what may be called psychogenic or psychosomatic rheumatism formed an object of study. Although belonging to the neuroses, this condition bears a relation to the handling of joint disease that is even more important under military conditions than in civilian life. Low-back pain was excluded from consideration, unless actually due to arthritis or forming a part of the symptomatology of the arthralgia or psychogenic rheumatism group. Finally, rheumatic fever, although having certain features in common with rheumatoid arthritis and occasionally mistaken for one of the arthritides, was regarded as an independent, generalized disease and was therefore considered only in the differential diagnosis.

Material for this study was gathered from epidemiologic data available at the offices of the Surgeon, Fifth Army, and of the Theater Surgeon, from hospital records, by questionnaires sent to general hospitals, by conferences with medical officers throughout the Theater and by personal observations.

*The following material represents a condensation and a certain amount of revision of parts of a clinical monograph on arthritis prepared at the direction of the Surgeon, Mediterranean Theater of Operations, United States Army, and submitted to him in final form in June, 1945.

INCIDENCE OF ARTHRITIS

No over-all figures were available to determine the incidence of the arthritic diseases† among American troops in the Theater. Samples, chiefly from hospital admissions, dispositions or patients remaining, however, were utilized to give a rough indication of the extent of the problem. The six evacuation hospitals serving the Fifth Army in August, 1944, are considered first. During one week 2149 soldiers were admitted to these hospitals for disease. Those complaining of nontraumatic musculoskeletal disorders numbered 128, or 3.4 per cent, of the total. The dispositions to duty or to the base for the month of August, 1944, are shown in Table 1. Although the arthritic diseases made up only a small proportion of either the weekly (3.4 per cent) or the monthly (3.1 per cent) dispositions, it is possible that the incidence would have been increased in figures obtained during months of rain and cold.

Table 2 presents the breakdown of medical admissions to a station hospital from August, 1943, through April, 1945. Again, conditions grouped under the heading "arthritis" made up a small proportion of the total — 6.5 per cent of the noninfectious cases and 1.8 per cent of the total admissions to the medical service. When the arthritic patients admitted to general hospitals were enumerated, the rate was somewhat higher — 1.8 per cent of total admissions and 4.1 per cent of patients entering the medical services (Table 3). Comparable figures were obtained from a study of the cases remaining in hospitals in the Peninsular Base Section on a given day of each month from March through November, 1944. The arthritic cases, including arthritis, myositis and myalgia, in the musculoskeletal group were separated from the remainder, consisting chiefly of low-back pain, pes planus and bone disease (Table 4). A daily average of 343 patients with arthritic diseases were hospitalized in this base section, making up 3.3 per

†In this section, the term "arthritic diseases" includes in both text and tables conditions diagnosed as arthralgia, myalgia, myositis and fibrositis.

cent of the total of those with disease and 4.7 per cent of those with noncommunicable disease. On the basis of the percentage obtained in Table 4 an estimate was made of the man-days lost through hospitalization for arthritis in the Theater during 1943, 1944 and the first four months of 1945 (Table 5). The figure obtained was 275,000 man-days for this period of twenty-eight months.

TABLE 1. *Dispositions to Duty or to the Base from Six Evacuation Hospitals Serving the Fifth Army in Italy during August, 1944.*

TYPE OF DISEASE	NO. OF CASES	PERCENTAGE	RATE PER 1000 PER ANNUM
Gastrointestinal	1,147	15.3	88
Genitourinary	1,005	13.1	77
Skin	936	12.4	72
Respiratory	672	8.8	52
Neuropsychiatric	631	8.3	49
Eye, ear, nose and throat	530	7.3	40
Cardiovascular	333	4.5	25
Musculoskeletal, nontraumatic	235	3.1	18
Musculoskeletal, traumatic	171	2.2	13
Miscellaneous (malaria, sand-fly fever and so forth)	1,912	25.0	150
Totals	7,572		584
Accidental injuries	1,235		97
Grand totals	8,807		681

The importance of arthritis as a cause of manpower loss was more significantly measured by the number of soldiers rendered unavailable for combat owing to reclassification for limited service or removed entirely from the Theater by evacuation than by the morbidity figures given alone. The liability of the arthritic patient to escape returning to full duty was suggested, however, by the slightly increased rate (4.1 per cent) found on the medical services of three general hospitals (Table 3), compared with figures from other types of hospitals and for those in the Peninsular Base Section as a group. Any medical patient, of course, was less likely to return to full duty once in a general hospital but the data considered below demonstrate that a high percentage of those with joint disease failed to resume their previous duty status. Table 6 presents the combined figures for dispositions of patients with arthritis from ten general hospitals as obtained from written questionnaires and from the records of the Medical Service of the Forty-Fifth General Hospital, with the period covered chosen to exclude the time when this hospital was receiving many patients from other general hospitals for evacuation. For comparison, the ratios of dispositions of the remainder of the medical patients in this hospital and of all patients hospitalized for disease in the Theater are presented. The inference can be drawn from this table that nearly half the patients with arthritis reaching a general hospital in the Theater were evacuated, another fourth being reclassified for limited service, and that the incidence of evacuation and reclassification was greater among arthritic patients than among the run of medical patients.

TABLE 2. *Classification of Patients Admitted to the Medical Service of the Seventy-Third Station Hospital (August, 1943, through April, 1945).*

TYPE OF DISORDER	NO. OF CASES	PERCENTAGE OF TOTAL ADMISSIONS	PERCENTAGE OF NONINFECTIOUS CASES
Noninfectious:			
Neuropsychiatric	669	4.9	18.3
Skin	607	4.5	16.6
Gastrointestinal	440	3.3	12.1
Arthritic	239	1.8	6.5
Miscellaneous	1,700	12.6	46.5
Totals	3,655	27.1	
Infectious	9,867	72.9	
Total	13,522		

TABLE 3. *Incidence of Arthritis in Admissions to Ten General Hospitals to December 1, 1944, and in Admissions to the Medical Service in Three.*

GENERAL HOSPITALS	TOTAL ADMISSIONS	CASES OF ARTHRITIS NO.	CASES OF ARTHRITIS PERCENTAGE
Ten general hospitals	177,317	3,260	1.8
70th General Hospital (Medical Service)	5,916	274	4.6
45th General Hospital (Medical Service)	12,259	467	3.8
12th General Hospital (Medical Service)	10,076	416	4.2
Totals	28,251	1,157	
Average			4.1

TABLE 4. *Average Number of Patients with Diseases Remaining in Peninsular Base Section Hospitals on a Given Day Each Month (March through November, 1944).*

TYPE OF DISEASE	NO. OF CASES	PERCENTAGE OF TOTAL DISEASES	PERCENTAGE OF NONCOMMUNICABLE DISEASES
Noncommunicable:			
Surgical	1,327	12.9	18.4
Neuropsychiatric	1,315	12.8	18.2
Liver and gall bladder	872	8.4	12.0
Skin	676	6.5	9.4
Arthritis	343	3.3	4.7
Other musculoskeletal	333	3.2	4.6
Genitourinary	298	2.9	4.1
Gastrointestinal	265	2.6	3.6
Ear	220	2.3	3.0
Eye	198	1.9	2.7
Cardiovascular	153	1.5	2.1
Dental	139	1.3	1.9
Allergic	81	0.8	1.1
Miscellaneous	1,032	10.0	14.2
Totals	7,252	70.4	
Communicable	3,119	29.6	
Grand total	10,371		

It was not possible to gather extensive data regarding the disposition of arthritic patients from other installations than general hospitals. How many of the 235 soldiers with joint disease discharged from Fifth Army evacuation hospitals during August, 1944 (Table 1), returned to duty was not available, but an indication was furnished from the records of the Third Convalescent Hos-

pital. Officers from this hospital made up the Disposition Board for the Fifth Army. A total of 3991 patients with various conditions were reclassified for limited service between February 22, 1944, and May 1, 1945 (Table 7). The importance of arthritis is evident from these data, since these patients constituted the largest group among those reclassified for disease and were surpassed in the whole number only by neuropsychiatric cases and battle casualties.

TABLE 5. *Man-Days Lost through Hospitalization in the Mediterranean Theater.*

PERIOD	MAN-DAYS LOST			AVERAGE NO. OF ARTHRITIC PATIENTS IN HOSPITAL
	TOTAL	FOR ARTHRITIS	FOR DISEASE	
1943	4,036,000	89,000	2,704,000	244
1944	6,580,000	145,000	4,387,000	398
January to April, 1945	1,871,000	41,000	1,247,000	341
Totals	12,487,000	275,000 (2%)	8,338,000 (67%)	

During World War I, a total of 65,192 patients suffering from joint disease (exclusive of rheumatic fever) were admitted to Army hospitals.[1] Until the data for World War II are finally compiled, no comparison is possible, but owing to the greater size of the Army alone, it is probable that the total figure will be at least doubled. In 1941 about 35,000 veterans disabled by arthritis were receiving compensation, including, of course, those whose illness had started after discharge from the service. As yet, little has appeared in the literature on the military incidence of joint disease in World War II. The admissions to two British general hospitals in France in 1940 (during a period of combat inactivity) indicated a much higher incidence of arthritic disease in the British Army at that time than in the United States Army in the Mediterranean Theater.[2] In fact, 10 per cent of all those patients admitted to hospitals and 20 per cent of those entering the medical service referred their symptoms to the joints or other supporting structures (fibrositis). The experience of the Medical Division of a United States Naval Base Hospital operating at Casablanca in 1943 and 1944 has recently been published.[3] In the first year of operation, 36 cases (4.8 per cent) among 744 admissions were diagnosed as arthritis, a proportion corresponding to that obtained in the three Army general hospitals cited in Table 3. Kinsey[4] analyzed a series of 1000 patients separated

TABLE 6. *Disposition of Patients with Arthritis in General Hospitals Compared with That of Other Medical Patients.*

SOURCE	TOTAL	DUTY		LIMITED SERVICE		EVACUATION	
		NO.	PER-CENTAGE	NO.	PER-CENTAGE	NO.	PER-CENTAGE
Arthritis:							
Ten general hospitals (up to December 1, 1944)	2,938	956	32.6	692	23.4	1,290	44.0
45th General Hospital (Medical Service)	329	63	19.1	130	39.6	136	41.3
Diseases other than arthritis:							
45th General Hospital (Medical Service)	5,222	3,341	64.1	534	10.2	1,347	25.7
Patients hospitalized for disease in Theater (January, 1943, to April, 1945)*	703,320	618,921	88.0	53,079	7.6	31,320	4.4

*Includes arthritic patients.

The number of patients evacuated from the Theater for arthritis may be estimated from a sample containing the distribution according to diagnoses of evacuees for disease from the Mediterranean Base Section from March 1 to June 1, 1944. (During this period most of the patients going to the Zone of the Interior from the Theater left via this base section.) If neuropsychiatric disorders were excluded, arthritis was outnumbered only by peptic ulcer and outranked such conditions as pulmonary tuberculosis, rheumatic fever with or without valvular heart disease, trench foot, asthma, malaria and nephritis (Table 8). The patients evacuated for disease from the Theater in 1943, 1944 and the first four months of 1945 numbered 31,320. Applying the ratio (5.0 per cent) found in Table 8 to this figure, the number evacuated for arthritis may be calculated at 1566. The true figure is somewhat higher, since the total until December 1, 1944, for this group of diseases from eleven of the fifteen general hospitals in the Theater amounted to 1507.

TABLE 7. *Distribution of Patients Classified for Limited Service by the Third Convalescent Hospital from February 22, 1944, to May 1, 1945.*

TYPE OF CASE	NO. OF CASES	PERCENTAGE OF TOTAL	PERCENTAGE OF DISEASE CASES
Neuropsychiatric	2,283	58.1	
Battle casualties (residual effects)	342	8.4	
Injuries	212	5.2	
Arthritis	284	7.0	24.8
Pes planus or pes cavus	237	5.7	20.8
Eye	133	3.2	11.5
Asthma or bronchitis	120	3.0	10.5
Ear	66	1.7	5.8
Trench foot	37	0.9	3.2
Miscellaneous.....	277	6.8	23.4
Total	3,991		

from the Army on certificates of disability for discharge in the last three months of 1942 at the Station Hospital, Camp Blanding, Florida. Patients with chronic arthritis made up 5 per cent of the total, and were outnumbered only by patients with psychoneurosis, duodenal ulcer and psychoses. In spite of such screening, which was probably representative of the training camps in the United States, arthritis constituted, as shown by the data presented in this section, one of the important causes of disability in troops overseas.

TABLE 8. *Patients Evacuated from Mediterranean Base Section because of Disease (March–June, 1944).*

DIAGNOSIS	NO. OF CASES		PERCENTAGE	DIAGNOSIS	NO. OF CASES		PERCENTAGE
Neuropsychiatric disorder:	1513		59.0	Circulatory disorder:	179		6.7
Psychoneurosis	699		27.4	Trench foot	55		2.1
Dementia praecox	427		16.4	Valvular heart disease	25		1.0
Psychosis	228		9.0	Other	99		3.6
Other	159		6.2				
Musculoskeletal disorder:	254		10.0	Disease of eye, ear, nose and throat:	92		3.6
Arthritis	128		5.0	Otitis media	26		1.0
Rheumatic fever	63		2.5	Other	66		2.6
Other	63		2.5				
				Miscellaneous:	123		4.8
Respiratory disease:	210		8.2	Malaria	34		1.3
Tuberculosis	88		3.0	Nephritis	32		1.2
Asthma	49		2.4	Dermatosis	23		1.0
Other	73		2.8	Other	34		1.3
Gastrointestinal disease:	194		7.7				
Peptic ulcer	169		6.7				
Jaundice	15		0.6				
Other	10		0.4				

TYPES OF ARTHRITIS

The "Index of Standard Diagnoses" generally used in Army hospitals did not, until amended, encourage an attempt at an exact diagnosis of the arthritides of unknown cause. Under Diagnosis 0750, the medical officer was not asked to specify whether he was dealing, for example, with rheumatoid or hypertrophic arthritis. In some hospitals, additional diagnoses were provided for this purpose, but in others any such subdivision was left to the initiative of the ward officer. The written questionnaire sent to general hospitals was drawn up with this point in mind, and headings were provided for both acute and chronic arthritis, type unspecified, as well as for rheumatoid and hypertrophic arthritis. Arthralgia, myositis and myalgia were believed to be the most frequent terms used for this group of cases, although some have undoubtedly been listed under fibrositis or variations of that term. For these reasons no exact information is available regarding the types of arthritis seen in the ten general hospitals, combined figures from which were obtained from answers to the questionnaire, but the large size of the arthralgia-myositis group, which exceeded any of the others, is apparent (Table 9). The disposition of each type is also expressed in this table, although the figures are, of course, not of great significance on account of the groups with type unspecified. As might be expected, they show a trend toward return to duty in the acute and infectious groups and demonstrate clearly the more favorable outcome in the arthralgia group as compared to that in the cases of real arthritis.

Table 10 presents a classification of the patients with arthritis discharged from the Medical Service of the Twelfth General Hospital. The opportunity was presented of examining the discharge summaries of all the patients enumerated and formulating an opinion concerning the correct diagnosis when the type of arthritis was unspecified or when the diagnosis seemed at variance with the facts available. The breakdown into types of arthritis was therefore revised and was not entirely in accord with the medical records or with the Army nomenclature. Owing to the completeness of the records of this hospital, a group of cases labeled "psycho-

TABLE 9. *Disposition of Patients with Arthritis in Ten General Hospitals to December 1, 1944 (as Obtained from Questionnaires).*

DIAGNOSIS	TOTAL CASES	DUTY		LIMITED SERVICE		EVACUATION	
		NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE
Arthritis:	2,020	418	20.7	429	21.2	1,173	58.1
Rheumatoid	393	85	21.3	44	11.2	264	67.5
Hypertrophic	621	66	10.6	170	27.4	385	62.0
Chronic (type unspecified)	787	177	22.5	189	24.0	421	53.5
Acute (type unspecified)	159	70	44.0	17	10.7	72	45.3
Other (chiefly infectious)	60	20	33.3	9	15.0	31	51.7
Arthralgia	497	242	48.6	187	37.6	68	13.8
Myositis, myalgia	421	296	70.2	76	18.0	49	11.8
Totals	2,938	956		692		1,290	
Averages			32.6		23.6		43.8

genic rheumatism" are included in these figures, and the number of cases in this group, in addition to those in the arthralgia group, nearly equals the sum of the cases of definite arthritis.

Numerical data concerning the relative incidence of the various types of arthritis encountered in the Theater were available only from general hospitals. The impression gained, however, from conferences with medical officers in station and evacuation hospitals was that the patients with arthralgia made up by far the greatest proportion of those with joint symptoms. This opinion is reflected in the relatively large number of such patients in general hospitals, although in other installations many patients were returned to some form of duty and therefore never reached a general hospital. Figures from two British general hospitals in 1940, which were evidently acting chiefly as station hospitals (unqualified) and about a fourth, muscular rheumatism or myositis.[1] Gonorrheal arthritis comprised about 12 per cent of the cases of arthritis tabulated in World War I, probably exceeding in incidence, for reasons discussed below, this form of infectious arthritis in the Mediterranean Theater. Although there are variations in individual hospitals and in groups of hospitals, no significant difference in incidence in the Theater between rheumatoid and hypertrophic arthritis is discernible when the available figures are combined. In the two British general hospitals mentioned above, about twice as many patients with rheumatoid as with hypertrophic arthritis were tabulated[2] — a ratio confirmed in the United States by Kinsey,[4] whose study, however, was concerned only with patients separated from the service for disability. Boland and Corr's[5] results agree more nearly with those obtained in

TABLE 10. *Disposition of Patients with Arthritis on the Medical Service of the Twelfth General Hospital, to December 1, 1944.*

DIAGNOSIS	TOTAL CASES	DUTY		LIMITED SERVICE		EVACUATION	
		NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE
Arthritis:	157	11	7.0	24	15.3	122	77.7
Rheumatoid	72	7	9.8	12	16.7	53	73.5
Hypertrophic	51	1	2.0	10	19.6	40	78.4
Other (chiefly infectious)	34	3	8.8	2	5.9	29	85.3
Arthralgia, myositis and myalgia	101	26	25.8	27	26.9	48	47.3
Psychogenic rheumatism	51	4	7.8	30	58.8	17	33.4
Totals	309	41		81		187	
Averages			13.3		26.2		60.5

at that time, are in agreement, several times as many cases being classified as "fibrositis" as those with real arthritis.[2] In a study by Boland and Corr[5] of 450 consecutive cases diagnosed as arthritis or an allied organic condition before admission to the Medical Service of Hoff General Hospital, patients with rheumatoid or hypertrophic arthritis were outnumbered by those with psychogenic rheumatism. In this study the diagnosis of fibrositis was made infrequently, perhaps because of the care with which the authors investigated the possibility that emotional factors produced somatic symptoms in the musculoskeletal system. At the Army and Navy General Hospital at Hot Springs, Arkansas, the incidence of the various types of rheumatic disease based on 2000 consecutive admissions in 1944 was as follows: rheumatoid arthritis, 34.3 per cent; psychogenic rheumatism, 18.8 per cent; fibrositis, 13.6 per cent; hypertrophic arthritis, 12.4 per cent; gonorrheal arthritis, 1.4 per cent; and miscellaneous, 19.5 per cent.[6] The criteria governing the admission of patients to this hospital are not available, but it is significant that cases of fibrositis and psychogenic rheumatism made up about a third of the total number. The figures for World War I show that about half of 65,192 soldiers admitted for joint disease were labeled arthritis the Mediterranean Theater, although a slightly greater number of cases of rheumatoid arthritis were found, and nearly three times as many patients with rheumatoid as with hypertrophic arthritis were admitted to the Army and Navy General Hospital.

In conclusion, since exact figures are not available, the relative incidence of the various types of arthritis encountered in the Theater may be summed up briefly. Patients with joint symptoms but without objective changes were encountered more frequently than those with any of the organic types of arthritis. In many of this group, a psychogenic origin of symptoms was demonstrated when sought for. Among those with real arthritis, no significant difference in incidence was demonstrated between the rheumatoid and the hypertrophic types. Cases of specific infectious arthritis were relatively infrequent. The distribution was roughly as follows: arthralgia, 40 per cent; rheumatoid and hypertrophic arthritis, 25 per cent each; and specific infectious arthritis, less than 10 per cent (Table 10). So far as prognosis for return to duty was concerned, patients with arthralgia presented a much more favorable outlook than those in either the rheumatoid or hypertrophic groups.

Rheumatoid Arthritis

In this paper no attempt is made to present an inclusive description of rheumatoid arthritis derived from the literature or from observations in civilian practice. Instead, the more important aspects of the disease as seen in the Mediterranean Theater will be outlined, comparison being made, when indicated, with civilian experience. The name "rheumatoid arthritis" is used throughout, both for the sake of uniformity and because it was generally, if not universally, employed in the Theater. Rheumatoid spondylitis, although believed to be a variation of rheumatoid arthritis rather than an independent entity, and atypical forms are chiefly discussed for greater convenience in separate sections.

The age distribution in 132 consecutive cases of rheumatoid arthritis personally studied is presented in Table 11. About 75 per cent of patients were from twenty to thirty-four years of age, and the mean age was thirty years and nine months. Since the age distribution of the troops involved is not known, these figures give no clue regarding a predilection of the disease for any age group. A comparison may be made, however, with the mean age of thirty-four years and nine months in 101 cases of arthralgia and thirty-eight years and ten months in 51 cases with hypertrophic arthritis, both series having been obtained from the records of the Twelfth General Hospital.

Table 11. *Age Distribution of 132 Patients* with Rheumatoid Arthritis Studied in the Sixth General Hospital.*

Age Group	No. of Cases	Percentage
yr.		
15–19	0	0.0
20–24	29	22.0
25–29	30	22.8
30–34	39	29.5
35–39	18	13.6
40–44	11	8.3
45–49	5	3.8
50–54	0	0.0

*Mean age 30.8 years.

That the cause of rheumatoid arthritis is not yet known may be stated without further discussion. Precipitating factors in civilian series have been found to be infections (especially of the upper respiratory tract), trauma, exposure to cold and dampness and emotional stress. Such factors were elicited in a minority of the patients with an onset recent enough to make the history reliable. Nearly half the 132 patients in the series, however, definitely dated the onset of the arthritis or noted an exacerbation in a previously existent disease within two months following their landing in North Africa. These findings are difficult to evaluate but suggest a possible association of the course of the disease with the hardships and anxieties of overseas service or the unfavorable climatic conditions of the winter of 1942–1943.

Diagnosis and Clinical Features

There is no specific diagnostic test for rheumatoid arthritis, but the disease must be considered an entity, since both the clinical picture and the roentgenologic and pathological findings are unmistakable in advanced cases. Such patients, of course, with the exception of those with spondylitis, rarely escaped the screening process of induction and preliminary training and were only occasionally encountered in the Theater. The diagnosis of the disease under such conditions depended on the demonstration of a fairly characteristic total clinical picture, in addition to the exclusion of other forms of organic or functional joint disease. So far as the history is concerned, an inquiry into the previous existence or past attacks of joint disease is of primary importance. In the series of 132 patients, slightly over half gave a definite history of symptoms consistent with rheumatoid arthritis before induction and about two thirds gave evidence of the disease before arrival in North Africa. The disease had obviously started five to ten years previously in many cases and twenty years or more before admission in 5 patients. A history of previous attacks lasting from a few weeks to several months was usual (although about a third of the patients were in their first attack of less than a year's duration). The majority of patients who had had earlier attacks had never enjoyed a complete remission but continued to have morning stiffness and articular pains of varying severity but evidently insufficient to prevent induction and embarkation. As in civilian practice, the preceding attacks had often been erroneously labeled inflammatory rheumatism or rheumatic fever.

In the diagnosis of rheumatoid arthritis, it is essential to recall that one is dealing with a generalized disease exhibiting well marked constitutional manifestations. A history of easy fatigability, anorexia or weight loss was obtained in 87 per cent of cases in the Sixth General Hospital series, sometimes before the actual onset of arthritis. These symptoms, one or more of which could, of course, have been elicited from a large proportion of the soldiers in the Theater, were of less diagnostic value than in civilian practice, unless of a severe degree. Vasomotor instability, evidenced by cold extremities, often with increased sweating, was found in about two thirds of the patients in the series, and an equal number had numbness of the hands or feet, with paresthesias variously described as tingling, burning or stinging. Motor weakness, especially of the grips, and tremor were additional neurologic symptoms. Since many patients with rheumatoid arthritis had minimal articular signs, the presence of the symptoms listed above was of real diagnostic assistance.

Regarding physical examination, the consensus was that objective joint changes, chiefly swelling, were necessary for a definite diagnosis of rheumatoid arthritis involving the peripheral joints. One obvious exception to this rule occurred when swelling had previously been noted in the clinical record accompanying the patient in the process of evacuation. A careful check of the peripheral joint findings in the series of 132 patients with diagnoses of rheumatoid arthritis showed only 11 without evidence of articular swelling, 3 of whom had definite limitation of motion. The remainder fulfilled the diagnosis by characteristic symptomatology and by multiple and symmetrical joint involvement limited to tenderness and pain on motion. Another medical officer with a large experience in arthritis stated that he had also occasionally made the diagnosis of rheumatoid arthritis under these conditions. The tendency of the disease to be bilateral, often in a strikingly symmetrical fashion, is especially characteristic of rheumatoid arthritis. In this series of 132 cases, 87 per cent of patients with extraspinal involvement had at least one pair of corresponding joints affected. On the other hand, 12 cases were seen with entirely unilateral involvement of more than one joint, the duration in 6 averaging nearly ten years. One interesting finding by Boland,[7] in a general hospital in the United States, was not confirmed. In 70 per cent of his 41 cases of rheumatoid arthritis, the involvement was confined to the lower extremities. A check of 112 patients with peripheral arthritis in the Mediterranean Theater disclosed that the upper extremities alone were involved in 15, the lower extremities in 22 and both in 75. Similarly, Boland found 41 per cent with metatarsophalangeal and toe involvement in contrast to 10 per cent with arthritis of corresponding joints of the hands, whereas a study of the 112 patients in the Theater revealed an involvement of 30 per cent and 53 per cent respectively.

Weight loss, cold, clammy extremities, tremor, muscle atrophy and weak grips were also detected on physical examination. Iritis, which may be a manifestation of rheumatoid arthritis, or a history of this condition, was encountered in only 3 per cent of the series. Fever, with temperatures occasionally ranging as high as 102°F., was recorded in about a sixth of the patients. The incidence of splenomegaly, lymphadenopathy and rheumatoid nodules was much less than that usually observed in civilian practice, the nodules being found in only 5 per cent of patients with peripheral joint involvement. This difference was probably associated with the relative mildness of the disease: an estimate of the total severity in the series at the Sixth General Hospital showed the cases to be mild in 33 per cent, moderate in 60 per cent and severe in only 7 per cent.

Although no specific laboratory test for rheumatoid arthritis is known, the sedimentation rate has been found helpful diagnostically, chiefly in a confirmatory sense, and although it is recognized in civilian practice that a patient may have rheumatoid arthritis and a normal sedimentation rate, this group has been small and probably numbers less than 10 per cent. From examination of the case records at the Sixth and Twelfth general hospitals, the reverse was true. The rate was increased in only 52 per cent of 112 patients in the former series, and in 36 per cent of 52 patients on whom the test was performed in the latter. The difference may result from the more advanced type of case seen in civilian hospitals or because more accurate procedures, such as the Rourke–Ernstene method, have been employed than those generally used in Army laboratories (Wintrobe and Westergren). The white-cell count was variable and not of diagnostic importance, and few patients in the Theater showed an anemia consequent to the disease. It was generally agreed in the Theater that articular x-ray examination usually proved negative except in cases of rheumatoid spondylitis. In the Twelfth General Hospital only about a sixth of the patients with peripheral joint involvement showed changes (with the exception of soft-tissue swelling), whereas in the Sixth General Hospital 30 per cent evidenced varying degrees of bony atrophy and another 8 per cent, joint narrowing or destruction. The conclusion can thus be drawn that the diagnosis of rheumatoid arthritis in the stage usually encountered in the Theater generally had to be established by the clinical picture rather than by laboratory or x-ray study.

Differential Diagnosis

The majority of observers in the Theater stated that rheumatic fever was readily distinguished from rheumatoid arthritis. Acute types of rheumatoid arthritis, however, as well as rheumatic fever tending toward long-continued joint involvement, at times furnished difficulty. Usually the distinction between the two diseases could be made after several weeks' observation, but in any event, the indications for treatment and disposition were similar, irrespective of the final diagnosis. Hypertrophic arthritis was ordinarily easily differentiated from rheumatoid arthritis. Exceptions occasionally occurred in patients with hypertrophic arthritis showing a marked degree of synovitis and in those, usually in the older age groups, who had rheumatoid arthritis clinically but demonstrated hypertrophic changes on x-ray study. The distinction between rheumatoid arthritis and the conditions grouped under the heading of arthralgia proved especially difficult, even in cases in which the localization was apparently extra-articular. In general, the presence or absence of objective joint changes constituted the deciding factor, since, as mentioned above, the diagnosis of rheumatoid arthritis was rarely made in their absence. The sedimentation rate and x-ray examination were not of great value in this type of case,

except as a check on the clinical impression. Daily questioning of the patient, with careful examination of painful joints over a period of several weeks, often clarified the decision. When doubt finally existed and the patient's course remained stationary, the tendency was to abandon the diagnosis of rheumatoid arthritis for the time being and to return the soldier to some form of duty. In any patient with articular complaints without objective findings, the possibility of so-called "psychogenic rheumatism" was of course strongly suspected, and an attempt made to establish the presence of an underlying neurosis. Further details will be presented in a subsequent paper. Cases of traumatic arthritis were usually readily separated from those of rheumatoid arthritis except in the knee, where the physical finding of a dislocated meniscus or other injury was occasionally simulated by rheumatoid arthritis involving the joint. In such cases diagnostic joint aspirations and examination of the synovial fluid were apparently not utilized often enough. In certain patients in whom the joints of the feet were involved by rheumatoid arthritis, a diagnosis of foot strain was erroneously made at first.

Treatment

No specific treatment for rheumatoid arthritis has as yet been found, and none of those claimed to be specific without convincing evidence were tried in the Theater, including parenteral injection of gold compounds, massive doses of vitamin D and the use of autogenous or stock vaccines. A few patients were given fever therapy, usually with intravenous typhoid vaccine, without lasting beneficial results. Opinion was divided regarding the removal of focal infection. In a few hospitals, a rather thorough check for foci of infection was made. The results of removal or treatment of supposed foci were disappointing on the whole, although successes were reported in a few cases. In most patients, only obvious foci were removed — for example, the tonsils when the onset of the arthritis followed an acute tonsillitis or certain teeth when marked dental sepsis was present. Again, success in influencing the course of the disease was seldom attained. In well marked cases or those of long standing, the tendency was to evacuate the patient without an attempt at more than palliative treatment. In milder cases, especially those with early, acute involvement of one or a few joints, hospitalization was maintained until the patient could be returned to some form of duty or the chances of a remission seemed remote. Such patients were given general treatment, including bed rest, relief of pain and physical therapy, and were usually examined for focal infection.

Disposition

A compilation from ten general hospitals, with the elimination of those receiving many patients from other general hospitals for evacuation, revealed that about a fifth of the patients with the diagnosis of rheumatoid arthritis returned to full duty, the large majority of the remainder being evacuated to the Zone of the Interior (Table 9). The policies that governed this distribution may be summarized as follows. It was generally agreed that only an occasional patient merited a return to full duty, including those in their first acute attack with apparent complete subsidence and those of mild severity with duties that lent themselves to favorable living conditions, opportunities for rest and a chance for medical supervision. Some of the records examined, however, indicated that these conditions were not entirely fulfilled, and that further hospitalization would be necessary. Essentially the same conditions were laid down for limited service, except that a few hospitals determined this disposition more on the patient's ability to perform some kind of duty at the time of discharge than on the probability of his being able to continue a particular task. That more advanced cases and milder cases with repeated hospitalization should be evacuated was universally recognized — a fact that accounts for the high proportion of such dispositions.

Owing to the variability of the course of rheumatoid arthritis, it seems impossible to lay down rules for disposition that would finally prove applicable to every case encountered in overseas service. When the diagnosis is still in doubt, the soldier should certainly be returned to whatever duty he can perform at the time. But since the disease bears a definite threat of chronicity and long-standing disability, evacuation to the Zone of the Interior should provide the best chance for a relatively favorable outcome once the diagnosis has been established. Certainly, the hardships and anxieties of overseas service are likely to have a deleterious effect on the progress of the disease. Furthermore, it is not to the best interests of the service to return a man to duty who bears the liability or even probability of recurrence. From these considerations, although no figures for such recurrences are available, it is believed that, as with peptic ulcer and active pulmonary tuberculosis, evacuation is indicated in all but a few selected cases.

Atypical Rheumatoid Arthritis

Although rarer than the usual form of rheumatoid arthritis, an atypical form has been clearly defined in civilian practice. This variety appears acutely and at times follows a definite infection, usually of the upper respiratory tract. It is characterized by severe inflammation of one or a few joints in an asymmetrical fashion and may be accompanied by fever. Foci of infection of presumed etiologic significance are sometimes found, but any direct beneficial result from their removal is open to question, since remissions are more frequent and complete in this type than in the usual varieties of

rheumatoid arthritis. The diagnosis is established by the ruling out of specific infectious arthritis or gouty arthritis and by the later development of unmistakable rheumatoid arthritis.

This form was generally recognized in the Theater and comprised 18 per cent of cases with peripheral joint involvement in the series. The diagnosis was made under a varying terminology in addition to rheumatoid arthritis, but usually as "arthritis, infectious, cause undetermined." Proper emphasis was laid on the importance of eliminating a specific infectious arthritis by means of culture of the synovial fluid and examinations for genitourinary gonorrhea. A therapeutic test with chemotherapy was also a frequent procedure — in fact routine in some hospitals — but usually without definite effect on the course of the arthritis. Nevertheless, this condition tended to subside gradually, irrespective of treatment, and often went into a complete remission. If a remission took place, it seemed reasonable to discharge the patient to limited service or to duty in the Zone of Communications.

Rheumatoid Spondylitis

Since this variety of rheumatoid arthritis affects males about ten times as often as females and since its onset is most frequent in the second and third decades of life, a relatively large number of cases was expected in soldiers. This expectation has been fulfilled, according to available reports in the literature, the spinal type even outnumbering the peripheral type of rheumatoid arthritis in a British Army series and comprising 37 per cent of 89 patients with rheumatoid arthritis in a general hospital in the United States.[5] In the Mediterranean Theater the incidence was not so high, averaging 20 per cent of patients with rheumatoid arthritis at the Sixth General Hospital but lower in the records of other hospitals, where the condition was not especially looked for and was not always recognized when present. The diagnosis of rheumatoid spondylitis was made clinically with certitude in advanced cases with nearly rigid spines and later confirmed by the characteristic x-ray appearance of the sacroiliac joints. In earlier cases, it was confused at first with various types of organic and functional low-back conditions, and the diagnosis again was made by the bilateral, destructive changes seen in roentgenograms of the sacroiliac joints. A few cases were noted with the clinical picture of rheumatoid spondylitis, including marked constitutional symptoms, but with repeatedly negative x-ray examinations. In these patients, a presumptive diagnosis of rheumatoid spondylitis was made, without the opportunity of confirmation, since the symptoms were severe enough to warrant evacuation.

On account of the frequency of rheumatoid spondylitis in soldiers, x-ray examination of the lower back with careful interpretation of the sacroiliac joints seemed indicated in every patient with persistent back symptoms. In two small series examined in the Theater, 5 per cent and 10 per cent of patients, respectively, were found to have this condition, whereas in 181 cases with back complaints studied in a general hospital in the United States, 33, or 18.7 per cent, warranted a diagnosis of rheumatoid spondylitis.[5] The extent of the x-ray findings often seemed out of all proportion to the duration of the symptoms and the degree of disability. Not a few soldiers with advanced changes on x-ray examination fought through a campaign, including a parachutist who had made a number of jumps.

Summary

The general incidence of arthritis among American troops hospitalized for disease in the Mediterranean Theater was estimated to be relatively low (about 3 per cent), but approximately 275,000 man-days were lost for this reason from January, 1943, through April, 1945. As a source of permanent loss of man power from the Theater by evacuation or from combat troops by reclassification, arthritis was highly important.

Patients without objective evidence of joint disease nearly equaled in incidence those with evident arthritis. In general hospitals, the distribution was estimated as 40 per cent for arthralgia and psychogenic rheumatism, 25 per cent each for rheumatoid and hypertrophic arthritis and less than 10 per cent for specific infectious arthritis.

The onset of rheumatoid arthritis or an exacerbation was frequently noted following arrival overseas. A history of arthritis prior to induction was given in about half the cases, and before embarkation in about two thirds. Helpful points in diagnosis were a history of constitutional, vasomotor and neurologic symptoms and a finding of symmetrical joint involvement. The diagnosis of rheumatoid spondylitis was made in about a fifth of the patients with rheumatoid arthritis. Laboratory tests, including the sedimentation rate, and x-ray films were not of primary diagnostic value. The total severity of the disease was generally less than that noted in civilian hospitals. Difficulty was experienced in the differential diagnosis of arthralgia and psychogenic rheumatism. An attempt at treatment was made only in milder cases considered susceptible to remission. Only 20 per cent of patients with rheumatoid arthritis were returned to duty.

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THE PREVENTION OF POSTOPERATIVE PULMONARY EMBOLISM*

An Analysis of Fifty-Two Fatal Cases in Six Years

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INTEREST in venous thrombosis and pulmonary embolism has received great impetus in the past eight years by the simultaneous development of two methods of treatment — namely, venous section and ligation and anticoagulant therapy by heparin or dicumarol or by a combination of these anticoagulants. Unfortunately, in many minds the two methods have become competitive, whereas they should be complementary. There are definite indications for both procedures. It is readily conceivable that in many hospitals where adequate laboratory and clinical experience in the use of dicumarol is lacking, a precise and absolute control of the situation by femoral ligation is the method of choice. With more and more confidence, however, afforded by experience with anticoagulant therapy and statistical support from other workers in this field, in addition to our own, femoral ligations at the Lahey Clinic are, with few exceptions, limited to patients with venous thrombosis who must soon have a second-stage operation, to those with conditions such as hemorrhagic colitis in which an anticoagulant effect would be dangerous, to those with poor liver function and to those with ambulatory recurrence of phlebothrombosis with pulmonary embolism. If there is any hint of venous thrombosis, the present method of anticoagulant therapy is to start immediately with both heparin in Pitkin's menstruum and dicumarol. A single dose of heparin in Pitkin's menstruum prolongs the coagulation time before two hours have passed and protects the patient until a two-day latent period of dicumarol action has elapsed, by which time the prothrombin content has usually dropped. In the rare patient who is resistant to dicumarol the injections of heparin are continued every second day.

In the four years between January 1, 1942, and January 1, 1946, anticoagulant therapy was administered to 127 patients with postoperative venous thrombosis, with or without benign pulmonary embolism, with death in only 2. One patient had bilateral femoral vein ligation and only one dose of dicumarol. The other received inadequate doses of dicumarol and never obtained a prothrombin level within the therapeutic range; he was also given a transfusion, which destroyed the slight effect of the dicumarol, and died of a second pulmonary embolism a few hours later. After January 1, 1946, another fatal case occurred in a patient with postoperative phlebothrombosis treated by anticoagulant therapy. He had been extremely ill with peritonitis but later had a septic infarct in spite of adequate prothrombin reduction. This infarct ruptured and caused terminal pneumothorax and empyema.

Such a record, together with the experience of Barker[1] with dicumarol and of Loewe, Rosenblatt and Hirsch[2] with heparin in Pitkin's menstruum, compares favorably with reports of the prevention of pulmonary embolism by venous ligation and section.[3, 4]

These results represent a great advance in the prevention of pulmonary embolism once a warning venous accident has occurred in the form of venous thrombosis or a benign pulmonary embolism. In spite of this advance, death may occur from sudden or unrecognized pulmonary embolism — a situation that must be met by prophylaxis, which is still an important factor in any consideration of postoperative pulmonary infarct. We have therefore attempted to analyze 52 sudden, unrecognized or untreated fatal cases of pulmonary embolism in an effort to ascertain ways and means to reduce the mortality further. These deaths occurred from 1940 to 1946. Forty-eight of the fatal cases were postoperative among approximately 45,000 major surgical operations. In only 2 cases had thrombosis and embolism been recognized and the patient treated after a warning pulmonary embolism, as described above. Two deaths occurred in medical cardiac cases, and 1 patient died before contemplated surgery. Autopsy was performed in 21 cases. The remaining 31 patients gave ample clinical evidence of pulmonary embolism.

That prophylactic exercises are an important factor in the prevention of pulmonary embolism is suggested by a comparison of the number of deaths from pulmonary embolism in a year in two hospitals, in one of which bicycle exercises were faithfully supervised by the nursing staff, and in the other of which these measures had not yet been generally enforced; in the latter there were three times as many deaths from pulmonary embolism as in the former. Because of these figures, we now advocate wiggling of the feet a thousand times a day as being universally and immediately applicable to all types of surgical patients.

Figure 1 illustrates the incidence of death from pulmonary emboli according to age. The greatest incidence occurred in the sixth decade. Seventeen

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patients were between the ages of fifty-one and sixty years; 14 were in the seventh and 11 in the fifth decades. Thirty-three of the 52 patients were men, and 19 were women.

The surgical procedures are presented in Table 1. Extensive operations were performed on the stomach in 5 cases and on the large bowel — including a Miles or Mikulicz resection, colectomy and colostomy — in 19. Eight patients had pelvic operations, and if these are combined with the 19 cases in which surgery of the colon was performed, a group of 27 cases is formed, confirming the well known fact that thrombosis and embolism are likely to follow

TABLE 1. *Surgical Procedures Employed.*

OPERATION	NO. OF CASES
Miles resection (for carcinoma of rectum)	8
Mikulicz resection (for carcinoma of sigmoid)	6
Cholecystectomy	3
Transverse ileocolostomy (carcinoma of transverse colon)	2
Repair of uterine and rectal prolapse	2
Panhysterectomy	2
Gastroenterostomy and cholecystostomy	2
Mikulicz resection of terminal ileum, cecum and hepatic flexure	1
First-stage Lahey resection (for carcinoma of rectum)	1
Splenectomy and total gastrectomy	1
Colectomy	1
Subtotal gastrectomy	1
Gastrostomy	1
Resection of carcinoma of sigmoid (excision of involved loop and side-to-side anastomosis)	1
Cecostomy	1
Right pneumonectomy	1
Craniotomy (for brain tumor)	1
Suprapubic prostatectomy	1
Thoracotomy (for lung abscess)	1
Vesical diverticulectomy	1
Nephrectomy and ureterectomy	1
Synovectomy and revision of knee joint	1
Resection of frontal lobe	1
Bilateral oophorectomy	1
First-stage splanchnicectomy	1
Cervical laminectomy	1
Supraorbital neurectomy	1
Pyelotomy	1
Repair of diaphragmatic hernia and splenectomy	1
Exploratory laparotomy	1
Total	48

operations in the pelvis. Cranial operations in 3 cases and splanchnicectomy in 1 case were followed by fatal pulmonary embolism.

It has long been recognized that a history of previous vein trouble may predispose to venous thrombosis. Of 11 patients (22 per cent), 8 had varicose veins, and 3 a history of phlebitis. In 9 (17 per cent), no mention was made in the history of any previous vein trouble. This is a point in examination that should be most diligently sought for, as emphasized below.

The occurrence of postoperative pulmonary embolism according to the time elapsed after operation is summarized in Table 2. The period of greatest liability to the first pulmonary embolism was the sixth to the sixteenth postoperative day, 25 patients falling in this group. The first pulmonary embolus occurred before the sixth postoperative day in 11 cases and after the sixteenth day in 12.

The signs and symptoms associated with pulmonary embolism in the 52 cases are recorded in Table 3. Sagall, Bornstein and Wolff[5] pointed out that the clinical course of pulmonary embolism is punctuated by a series of events in which numerous signs or symptoms may be present. In the intervals there may be a complete absence of signs or complaints. It is further stated that on clinico-

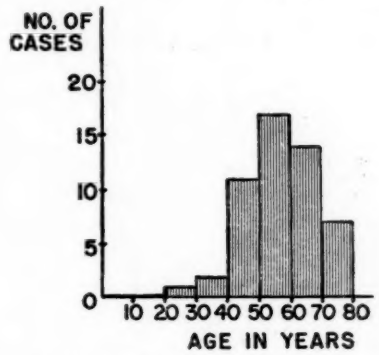

FIGURE 1. *Incidence of Death due to Pulmonary Emboli according to Age.*

pathological grounds each episode does not necessarily connote a separate pulmonary embolism. One embolus may be associated with several clinical episodes, and conversely, more pulmonary infarcts may be found at autopsy than can be accounted for clinically. The table demonstrates the frequency of elevated temperature, circulatory collapse, dyspnea, tachycardia, cyanosis and chest pain in thromboembolic disease. Chest pain, cyanosis and circulatory collapse have long been considered the earmarks of pulmonary embolism but they are only the most dramatic — not the most frequent — signs. Elevated temperature and tachycardia preceding the onset of dramatic symptoms are far more important warning signs.

The 52 cases were divided into three categories according to the time of death after the first symptoms of pulmonary embolism had been noticed.

TABLE 2. *Occurrence of Pulmonary Embolism according to Postoperative Day.*

POSTOPERATIVE DAY	NO. OF CASES
1	1
2- 5	10
6-10	13
11-15	12
16-20	7
21-25	2
30-37	3

This was done to determine if warning signs or symptoms were present, affording the clinician time to adopt preventive measures. Group 1 includes the sudden deaths or patients who died within an hour of the onset of pulmonary embolism; 22 cases (42 per cent) comprise this category. Group 2 was composed of patients who died within two to twenty-four hours after the first known pulmonary

incident (20 cases, or 38 per cent). Group 3 consisted of patients who died over twenty-four hours after the first signs of thrombosis and embolism (10 cases, or 19 per cent).

From the point of view of treatment, it might be assumed that the patients in Group 1 could not have been saved once the pulmonary embolism had occurred. A careful analysis of the record, however, disclosed the interesting facts presented in Table 4. In 16 of the 22 patients there was ample warning before death to permit adequate prophylaxis, in the form of venous ligation or anticoagulant treatment. Fever or tachycardia, or both, had been present in 15 of these cases for an average of seven days before death. The last patient had fever, tachycardia and mental confusion for three days prior to the fatal pulmonary embolism. Of 5 patients in this category who had a history of varicose veins, 3 died without any warning in the hospital. This leaves only 3 of the 22 cases in which there were no warning signs or history of previous vein trouble.

Of the 20 patients in Group 2, warning signs of thrombotic processes were present in 18 (Table 5). Fever alone or in combination with one or more other signs occurred in these patients from four to seventeen days before the onset of the first known pulmonary episode. In addition, 2 patients gave a history of previous superficial phlebitis, and 2 had varicose veins. Only 2 in this group of 20 patients gave no premonitory signs or history of previous vein trouble.

It is instructive to review briefly the course of 2 patients in Group 2. One patient, a forty-seven-year-old woman, underwent an anterior gastroenterostomy, enteroenterostomy and cholecystostomy. On the fourteenth postoperative day superficial thrombophlebitis of the right leg developed. On the twenty-second postoperative day a deep venous thrombosis was detected in the left leg. She was then belatedly given dicumarol on successive days in doses of 200, 200, 100, 0, 100, 100, 0, 0, 0, 0, 100 and 100 mg. She was allowed to dangle her feet out of bed on the twelfth day of anticoagulant therapy. Furthermore, a transfusion, which neutralized what anticoagulant effect might have been present, was administered for supportive reasons that evening. The patient spent a confused night and died suddenly on the following morning. The prothrombin times during the course of treatment were 72, 100, more than 100, 105, 69, 85, 63, 105 and 100 per cent of normal. Since the patient had a so-called "therapeutic level" (below 65 per cent of normal) on only one day, the dosage schedule was obviously inadequate. Moreover, on the day the transfusion was given, the prothrombin time was 100 per cent of normal. The occurrence in rapid succession of thrombotic processes in both legs that occurred in this case supports the present practice of doing bilateral vein ligations even when the veins of only one extremity are clinically involved. Furthermore, the failure of dicumarol in rare cases to produce an adequate fall of the prothrombin percentage is a definite indication for venous ligation or persistence in the administration of heparin in Pitkin's menstruum.

The other case that stands out in this group from the viewpoint of prevention is that of a forty-two-year-old man who entered the hospital for a

TABLE 3. *Signs and Symptoms Associated with Pulmonary Embolism in 52 Cases.*

Sign or Symptom	No. of Cases
Elevated temperature	37
Circulatory collapse	31
Dyspnea	30
Tachycardia	24
Cyanosis	24
Chest pain	12
Disorientation	6
Physical signs in chest	5
Coma	4
Hemoptysis	3
Positive roentgenologic findings	4
Positive electrocardiographic findings	2
Epigastric pain	2
Cough	1
Nausea	1
Vomiting	1
Pain in back	1
Pain in groin	1
Weakness	1
Incontinence	1
Dilatation of pupil	1
Convulsions	1

TABLE 4. *Warning Signs in Patients Dying One Hour after Onset of Pulmonary Embolism.*

Sign or Signs	Average Duration	No. of Cases	Cases with History of Venous Trouble
	days		
Fever	7	11	2 (varicose veins)
Fever and tachycardia	7	4	—
Fever, tachycardia and mental confusion	3	1	—
None	—	6	3 (varicose veins)
Totals		22	5

TABLE 5. *Warning Signs in Patients Dying within Two to Twenty-four Hours of Onset of Pulmonary Embolism.*

Sign or Signs	Average Duration	No. of Cases	Cases with History of Venous Trouble
	days		
Fever	4	1	—
Fever and tachycardia	6	7	1 (varicose veins)
Fever and venous thrombosis	8	1	1 (superficial phlebitis)
Fever and venous thrombosis, warning embolism and electrocardiographic changes	17	1	—
Fever, cyanosis and dyspnea	4	2	1 (varicose veins)
Fever and chest pain	6	3	—
Tachycardia alone	10	1	—
Disorientation	½	1	—
Fever and abdominal pain	6	1	1 (superficial phlebitis)
None	—	2	—
Totals		20	4

suspected mass in the right lung. In the four days between the time he was first seen and his entry into the hospital, a mild superficial bilateral thrombophlebitis had developed, for which ace bandages were applied. Two weeks later a right pneumonectomy was performed. On the seventh day after operation a low-grade fever developed, and on the eighth day the patient complained of soreness in the thighs along the course of both saphenous veins; the latter subsided in three days, but a mild nonproductive cough developed. On the sixteenth postoperative day, after being up for two days, he was suddenly stricken with dyspnea and cyanosis. Roentgenologic examination confirmed a clinical diagnosis of pulmonary infarct. While arrangements for a bilateral femoral ligation were being made, he suddenly became cyanotic, gasped for breath and died. Post-mortem examination revealed pulmonary embolism as the direct cause of death.

TABLE 6. *Warning Signs in Patients Dying over Twenty-four Hours after Onset of Pulmonary Embolism.*

SIGN OR SIGNS	AVERAGE DURATION	NO. OF CASES	CASES WITH HISTORY OF VENOUS TROUBLE
	days		
Phlebothrombosis and benign pulmonary embolism following coronary occlusion	7	1	1 (superficial phlebitis)
Phlebothrombosis and benign pulmonary embolism (1 patient treated*)	24	2	—
Multiple pulmonary emboli, positive electrocardiographic† and x-ray findings, fever and chest pain	8	1	—
Fever and multiple lung abscesses	7	1	—
Benign pulmonary embolism (mistaken for postoperative atelectasis)	8	1	—
Fever, tachycardia, dyspnea and shock	4	2	—
Fever, benign pulmonary embolism and positive x-ray findings	4	1	1 (varicose veins)
Fever and benign pulmonary embolism	5	1	—
Totals		10	2

*Warning signs recognized after two days, but treatment not given because the patient had a hopeless cancer.

†Electrocardiogram positive for cor pulmonale.

Group 3 included 10 cases (Table 6). The actual interval between the benign and the fatal embolism was one to twenty-four days. It is in this group that the most time naturally occurred for the institution of active therapeutic measures if warning signs and symptoms had been properly heeded. Two of the 10 patients gave a previous history of vein trouble, one having had varicose veins, and the other a superficial phlebitis. A third patient was not treated because of a hopeless carcinoma. A fourth patient was treated inadequately by anticoagulant therapy (the second patient treated in the entire group of 52 cases).

This patient was a sixty-two-year-old man who was admitted to the hospital in 1943 for a contemplated nephrectomy for carcinoma of the kidney. On admission, he gave evidence of a bilateral phlebothrombosis and benign pulmonary embolism. Bilateral femoral ligation was performed, and only one dose (200 mg.) of dicumarol was given. Later that day there was hemorrhage from the right femoral ligation. The vein was retied, and the anticoagulant therapy discontinued. The prothrombin time never dropped to a bleeding level, much less to the therapeutic anticoagulant level. Pulmonary sepsis developed, and the patient died two weeks later of a second pulmonary embolism. Autopsy showed old and recent pulmonary emboli and thrombi in the iliac veins but none in the inferior vena cava. Later experiences indicate that this patient might have been saved by either ligation of the inferior vena cava or energetic anticoagulant therapy.

TABLE 7. *State of the Legs Postoperatively in 48 Surgical Cases.*

GROUP OF CASES	POSTOPERATIVE EXAMINATION OF LEGS		
	NO MENTION	POSITIVE FINDINGS	NEGATIVE FINDINGS
1 (death in 1 hour)	14	0	8
2 (death in 2–24 hours)	6	3	9
3 (death over 24 hours)	5	2	1
Totals	25	5	18

Another patient in Group 3 whose history points a moral was a fifty-nine-year-old woman on whom a cholecystectomy was performed in 1940. On the thirteenth postoperative day she complained of pain in the left lower chest that was aggravated by breathing; a diagnosis of pulmonary infarction was made. The temperature rose to 100°F. on the day before the infarction occurred and continued at that level until the eighteenth postoperative day, when the patient suddenly died while being given a bed bath. There was no note in the record of any leg examination postoperatively. In 1940 the treatment of choice would have been femoral-vein ligation if the legs had shown any evidence of thrombosis. At present, the legs would be routinely examined in the presence of postoperative fever, and anticoagulant therapy begun.

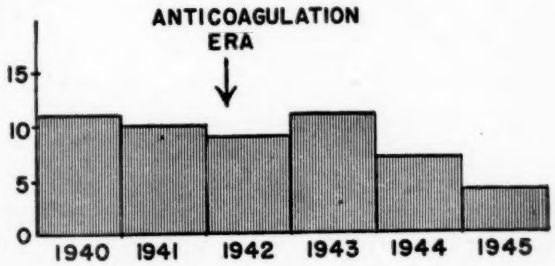

FIGURE 2. *Incidence of Death due to Pulmonary Emboli according to Year.*

Routine postoperative examination of the legs for evidence of phlebothrombosis should be carried out after all major surgical operations. This should

consist of careful questioning of the patient for pain in the legs, especially in the calf muscles. Even when a negative reply is given, the calf should be tested for tenderness, and an attempt made to elicit Homans's sign. Whether or not the legs were examined postoperatively in 48 surgical cases, and if so, the findings are listed in Table 7. The case records contained no mention of postoperative examination of the legs in 25 patients. Of the 23 patients who were examined, the evidence of peripheral-vein thrombosis was positive in 5 and negative in 18. It is probable that in some of the 25 cases in which no mention of examination of the legs was made, signs of phlebothrombosis of the leg veins might have been demonstrated.

TABLE 8. *Composite Data in Entire Series of 52 Cases.*

GROUP	NO. OF CASES	CASES WITH HISTORY OF VENOUS TROUBLE	POSTOPERATIVE EXAMINATION OF LEGS			WARNING SIGNS BEFORE FATAL EMBOLISM
			NO MENTION	POSITIVE FINDINGS	NEGATIVE FINDINGS	
1 (death in 1 hour)	22	5	14	0	8	16
2 (death in 2-24 hours)	20*	4	6	3	9	18
3 (death over 24 hours)	10†	2	5	2	1	10
Totals	52	11	25	5	18	44

*One of these cases was medical.
†One of these cases was medical; another occurred in a patient who died before operation.

A composite picture of the entire series of 52 fatal cases is presented in Table 8. In these cases no measure to prevent pulmonary embolism was deemed justifiable in 1 patient with inoperable carcinoma. The most noteworthy and indeed surprising fact demonstrated, however, is that 44 of 52 patients gave warning of thrombotic processes. This means that in 85 per cent of the cases death from pulmonary embolism might have been prevented if the warning signs had been appreciated and prophylactic measures undertaken. Even 73 per cent of those patients who died of pulmonary embolism within an hour had given some warning signs, such as fever and tachycardia, several days before the fatal embolism. Since early 1942 anticoagulant therapy has been the treatment of choice at the Clinic for phlebothrombosis, with or without benign pulmonary embolism, and for thrombophlebitis; because of this there has developed a stimulus to be wary of thrombotic emergencies, and it is gratifying to note the drop in mortality that has occurred. In Figure 2 the mortality per year is tabulated in the 52 cases studied from 1940 to 1946. Little change is apparent in the first two years (1942 and 1943). The small number of deaths in 1944 and 1945 reflect the clinician's trend to become more conscious of thrombosis and embolism. It may now be possible to achieve a deathless year in cases of pulmonary embolism. That this objective may be closely approached seems possible on a review of the 4 fatal cases in 1945, only 1 of which can strictly be classified as nonpreventable. This case was that of a seventy-six-year-old woman in whom a supraorbital neurectomy had been performed for right supraorbital neuralgia. Eight hours later she became cyanotic, the respirations were irregular, and she died within an hour. There was no warning of this embolism.

The first of the other 3 fatal cases in 1945 occurred in the patient described above as the second patient in Group 2. He had had repeated venous thromboses in the leg and a benign pulmonary embolism before femoral ligation was decided on. While being prepared for the procedure he died.

The third death in 1945 occurred in a fifty-two-year-old man in whom a Miles resection had been performed for carcinoma of the rectum. On the morning of the second postoperative day he became disoriented, and ten hours later lapsed into coma, with convulsions and dilatation of the right pupil. Pulmonary embolism was entirely unsuspected, and no antithrombotic measures had been undertaken. Autopsy revealed a large embolism in the main pulmonary arteries and tiny thrombotic fragments in the pelvic veins, probably attributable to the operative site.

The fourth fatal case in 1945 was that of a fifty-three-year-old man on whom a Miles abdominoperineal resection had been performed for carcinoma of the rectum. Wound evisceration occurred on the fourth postoperative day. The day after repair he went into shock and became cyanotic and dyspneic. He was treated for shock, peritonitis and atelectasis (by bronchoscopy). Two days later he died. No mention was made of examination of the legs postoperatively. The diagnosis of pulmonary embolism was apparently not entertained. Autopsy revealed atelectasis and peritonitis, but the direct cause of death was pulmonary embolism; thrombosis of the left common iliac vein was also observed.

SUMMARY

In a review of 52 fatal cases of postoperative pulmonary embolism the greatest number occurred in patients fifty to sixty years of age. Fifty-four per

cent of the deaths occurred after extensive pelvic or lower abdominal surgery, or both. This poses the question of routine prophylactic administration of heparin in Pitkin's menstruum and dicumarol shortly after such major surgical procedures.

The variability of the signs and symptoms associated with pulmonary embolism emphasizes the fact that a thrombotic process should be suspected postoperatively in every case of fever or tachycardia, or both.

Fifty-two per cent of the initial pulmonary emboli occurred between the sixth and sixteenth postoperative days, although a sufficient number occurred before and after that period to make one continuously on the alert for trouble.

Routine, careful examination of the legs postoperatively is required for evidence of phlebothrombosis.

Complete co-operation between the surgeon and the internist is essential to adequate therapy, whether it consists of anticoagulants or surgical ligation of the veins.

In 85 per cent of the 52 fatal cases, some preventive measure was indicated by premonitory signs, usually in the form of elevated temperature or tachycardia, or both, occurring a sufficient time before the fatal embolism to allow adequate therapy to be administered.

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NEUROPATHIC FOOT LESIONS IN DIABETES MELLITUS*

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JOINT changes associated with diseases of the central nervous system were first described by Charcot. At first these changes were considered peculiar to tabes dorsalis and syringomelia, but with extensive use of x-ray examination, similar changes have been found in other conditions. Leprosy may produce a similar picture, as may injury to a peripheral nerve, as described by Weinberg[1] in soldiers injured in World War I. Bone lesions similar to those in Charcot's joints have also been reported in association with diabetes mellitus.[2–7]

This report deals with neuropathic foot lesions that occur in patients with diabetes mellitus and are attributed to the effect of the diabetes on the nervous system. Seventeen cases of neuropathic foot lesions have been detected among approximately 20,000 consecutive cases of diabetes — an incidence of 1:1100. Additional cases have probably escaped recognition.

The earliest gross change detected in the foot with a diabetic neuropathic lesion is a unilateral or bilateral thickening of the tarsal region. No fluid is present in the joint. The swelling is painless, and no redness of the skin, heat or other signs of inflammation are present. These changes progress slowly and usually result in a thickened, deformed foot with a tendency to eversion and external rotation and a flattening of the longitudinal arch.

On roentgenologic examination the neuropathic foot is similar to the chronic Charcot joint of syphilis except that the destruction is chiefly limited to the tarsal and proximal ends of the metatarsal bones. The phalanges may also atrophy and become spindle shaped (Fig. 1). The characteristic appearance is a fragmentation and destruction of the metatarsal and the tarsal bones. The joint spaces disappear as

Figure 1. *Case 5.*

This x-ray film of the right foot shows destruction of the forward end of the astragalus and of most of the other tarsal bones, with soft-tissue swelling.

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their cartilage is lost, with a loss of continuity of the individual bones. Spontaneous fractures of the metatarsal bones may occur. Spur formation and destructive and proliferative. In Case 1 autopsy disclosed mild degenerative changes of all joint elements, characterized by small islets of bone destruc-

TABLE 1. *Data in 17 Cases of Neuropathic Foot Lesions among Diabetic Patients.*

Case No.	Sex	Age	Duration of Diabetes	Blood Hinton Reaction	Spinal-Fluid Wassermann Reaction	Spinal-Fluid Total Protein	Evidence of Diabetic Neuropathy	Roentgenologic Findings	Other Complications	Foot Involved
		yr.	*yr.*			*mg./100 cc.*				
1	F	29	20	Negative	Negative	19	Absent knee and ankle reflexes	Partial absorption, head of second metatarsal; first metatarsal irregular and dense.	Hypertension, albuminuria and retinitis proliferans	Left
2	F	67	19	Negative	—	—	Bladder paralysis and absent knee reflexes	Destruction and partial absorption of tarsal bones and metatarsophalangeal joints bilaterally	Slight hypertension, albuminuria and diabetic retinitis	Right and left
3	F	63	15	Negative	—	33	None	Destruction of first cuneiform and scaphoid bones; destruction and pathologic fracture of proximal end of third metatarsal.	Hypertension	Right
4	M	63	11	Negative	—	67	Absent knee and ankle reflexes	Destruction of joint spaces between tarsal and metatarsal bones; increased density of tarsal bones and of second metatarsal bone.	Slight hypertension and cataract	Left
5	F	56	14	Negative	Negative	100	Left peroneal paralysis, bilateral absent ankle reflexes and decreased sensation to pin point	Right: destruction of forward part of astragalus, most of the other tarsal bones and proximal ends of metatarsals. Left: similar, less pronounced changes.	Retinitis proliferans, albuminuria and coronary thrombosis	Right and left
6	M	59	11	Negative	Negative	60	Painful neuritis, anesthetic foot and loss of vibratory sense and sensation to heat and cold	Fragmentation and dissolution of continuity of the tarsal and proximal ends of metatarsal bones	Hypertension, albuminuria and diabetic retinitis	Right
7	M	30	7	Negative	Negative	61	Painful neuritis, paresthesias of feet, absent knee and ankle jerks and loss of vibratory sense in the feet	Half of scaphoid bone destroyed	Diabetic retinitis, hypertension and albuminuria	Right
8	M	63	14	Negative	—	59	Painful neuritis in arms and legs nine years previously	Proximal ends of 2nd and 3rd metatarsals and cuneiforms partially destroyed; anterior margin in cuneiform and scaphoid rough, irregular and dense.	Retinitis proliferans, cataracts (bilateral) and hypertension	Right
9	F	61	2	Positive	Negative	—	None	Anterior tarsal bones dense and their outlines lost; proximal ends of metatarsals irregular and eroded.	—	Left

lipping at the bone margins, characteristic of hypertrophic arthritis, are not seen.

Dr. Shields Warren examined histologically the foot lesions in Cases 1 and 6. In the latter a thigh amputation was necessary because of secondary infection. There was a complete loss of bone structure, numerous spicules of bone scattered throughout the area of involvement undergoing various stages of absorption and the remaining periosteum attempting to form new bone. These changes were partly obscured by the secondary infection. Thus, the lesion was like that in a Charcot joint, being both tion with an increase in the number of osteoblasts. There were foci of mild degenerative changes of the synovial structure, with numerous areas of round-cell infiltration. Increased vascularity was observed in the pericapsular tissue, the walls of the larger vessels showing some thickening. Examination of several sections of the peripheral nerves revealed no definite abnormality.

Clinical and Laboratory Data

Table 1 presents the pertinent data in these cases. In this series of 6 men and 11 women the average

age was fifty-six years at the time the foot lesion was discovered. The youngest patient was thirty and the oldest sixty-nine years of age. The diabetes had been present for an average of eleven and a half years.

An examination of the spinal fluid was performed in 15 cases. The Wassermann reaction was negative in all 12 cases in which the test was done. Colloidal gold tests were negative in 8 cases and showed a moderate elevation to the left in 2. The spinal-fluid protein was elevated in 11 of the 14 samples, averaging 69 mg. per 100 cc., with values of 100 mg. in 2 cases.

The blood Hinton test, which was negative in 15 cases, was positive in 2, in which the spinal-fluid serologic findings were negative. There was no clinical evidence of syphilis in any case.

Evidence of neuritis was found in 14 of the 17 cases. Absent knee jerks, foot drop, anesthetic feet, loss of sensation to pinprick and vibration, bladder paralysis and paresthesias of the lower extremities, especially a feeling of numbness, were the most frequent manifestations individually and in combination. Only 4 patients complained of the nocturnal pain in the extremities that often accompanies diabetic neuritis.

Hypertension was present in 15 of the 17 cases, and the systolic pressure exceeded 200 in 7 cases. A significant albuminuria (levels of over 100 mg. per 100 cc.) was recorded in 6 cases. Two patients

TABLE 1. *Data in 17 Cases of Neuropathic Foot Lesions among Diabetic Patients (Continued).*

Case No.	Sex	Age	Duration of Diabetes	Blood Hinton Reaction	Spinal-Fluid Wassermann Reaction	Spinal-Fluid Total Protein	Evidence of Diabetic Neuropathy	Roentgenologic Findings	Other Complications	Foot Involved
		yr.	yr.			mg./100 cc.				
10	M	43	11	Negative	Negative	35	Decreased sensation to pin prick and temperature changes and decreased vibratory sense in right foot	Proliferation and destruction of astragalus	Hypertension (mild)	Right
11	F	52	13	Positive	Negative	85	None	Destruction and proliferation of 3 cuneiform bones; proximal ends of 1st 4 metatarsals narrow; irregular joint spaces.	Hypertension, cataract (bilateral) and retinitis proliferans	Right
12	M	69	6	Negative	Negative	100	Anesthetic foot	Dense periosteal thickening of 4 lateral metatarsals; narrow tarsal joint spaces, with eburnation of joint margins.	Hypertension	Right
13	F	55	14	Negative	Negative	57	Absent knee reflexes	Marked loss of cartilage between metatarsotarsal and intertarsal articulations; irregular erosions of tarsal bones.	Hypertension, albuminuria and diabetic diarrhea	Right
14	F	61	8	Negative	Negative	42	Mild painful neuritis and loss of vibratory and pinprick sensation	Both feet: irregularity and destruction of proximal ends of all metatarsals and adjacent tarsal bones.	Hypertension and diabetic retinitis	Right and left
15	F	69	7	Negative	Negative	66	Absent ankle reflexes and slight knee reflexes	Destructive process involving tarsals and proximal ends of all metatarsal bones; tarsal bone margins dense.	Hypertension and diabetic retinitis	Right
16	F	45	18	Negative	—	—	Pupils irregular; no reaction to light in right pupil.	Destruction and condensation of distal end of 1st metatarsal; bases of all phalanges eroded; internal cuneiform and scaphoid roughened and dense; areas of absorption in proximal ends of 2nd and 3rd metatarsals.	Hypertension	Right
17	F	62	5	Negative	Negative	59	Loss of sensation to pin prick in terminal 10 cm. of left foot	Right: destruction of 1st, 2nd and 3rd metatarsals and first 4 toes. Left: similar changes in 1st metatarsal and first 4 toes. Both: complete disorganization of metatarsophalangeal joints	Hypertension, diabetic diarrhea and albuminuria	Right and left

had diabetic nocturnal diarrhea, which is considered a manifestation of diabetic neuropathy.

The eyes revealed diabetic retinitis in 9 of 15 cases, in 4 of which retinitis proliferans was distinguished by the ophthalmologist. The following is a typical case report.

CASE 6. W. W. (Case 10917) developed diabetes in 1931, when he was 48 years old. He was first seen in March, 1932, with a history of ascites on and off for 5 years. Peritoneal catheter drainage had been instituted at another hospital. The tube was removed, and closure of the abdominal wound followed in 3 months without subsequent recurrence; no acid-fast bacilli were demonstrated. The patient was given 5 units of regular insulin daily and a diet containing 155 gm. of carbohydrate, 71 gm. of protein and 97 gm. of fat (1777 calories).

He was not seen again until March, 1936, when the blood sugar was 520 mg. per 100 cc., and he confessed that he had been careless with his diet. He had developed moderately severe neuritis in the legs and back, with absence of knee and ankle reflexes. The blood pressure was 140/80. The pulsations in the dorsalis pedis arteries were normal. There was no demonstrable leg weakness. The pains and paresthesias in the legs and feet, which were much worse at night, gradually subsided after treatment of the diabetes for several months and with supplementary vitamins. Routine x-ray examination of the left foot disclosed a fragmentation and dissolution of continuity of the tarsal and proximal ends of the metatarsal bones. The foot was thickened grossly, and there was flattening of the longitudinal arch. A diagnosis of neurotrophic foot was made.

In November, 1937, osteomyelitis of the left ankle and a spreading infection required a guillotine amputation followed in 1 month by a left thigh amputation from which the patient made an uneventful recovery. Histologic examination revealed a loss of bone structure and of continuity of the tarsal bones, spicules of bones undergoing absorption and the remaining periosteum attempting to lay down new bone. The joint spaces were lost.

On this hospital admission intermittent nocturnal diarrhea, often with nocturnal fecal incontinence, was first noticed. Examination of the urine revealed a slight trace of albumin, and the blood sugar was 450 mg. per 100 cc. on admission. The serum protein was 6.6 gm. per 100 cc., with a reversal of the albumin-globulin ratio (0.74). The blood pressure was 150/90.

A year later the patient was again hospitalized with an infected callus on the right foot. A fluctuating blood pressure reached 192/110. There was a loss of vibratory sense in the lower half of the right leg and foot and a loss of sensation for hot or cold. The spinal-fluid Wassermann reaction, colloidal gold test and cell count were normal. On repeated examination 10 days later the total protein was 112 mg. per 100 cc. He was discharged on December 18, the foot having healed. The nocturnal diarrhea persisted intermittently.

In March, 1939, the patient was readmitted with infection of the bone of the 4th and 5th right toes that required incision and drainage. At that time the neuritis had become much worse and the nocturnal diarrhea had persisted. He stated that the diabetes had been under poor control while 20 units of protamine zinc insulin were being taken. Knee and ankle reflexes remained absent. The infection responded after incision and drainage of the foot, which was done without anesthesia since he had loss of pain sensation in the foot — a so-called "anesthetic foot." He made a gradual recovery.

In January, 1941, the patient was readmitted to the hospital having received a burn on the side of the foot from a heater — the anesthesia had prevented his realizing the excessive heat. He recovered with conservative treatment. Examination of the urine revealed a quantitative albumin of 0.8 gm. per 100 cc. On admission the blood sugar was 330 mg. per 100 cc. On discharge the patient was advised to take 36 units of protamine zinc insulin daily.

He was readmitted in November, 1941, complaining of edema of the ankle of several months' duration, dyspnea on slight exertion and orthopnea. The blood pressure was 180/106. Cardiac enlargement with an apical systolic murmur was found, and there was a small bilateral pleural effusion. The urinary sediment contained many white cells, and a phenolsulfonephthalein test showed 19 per cent excretion of the dye in 2 hours. The congestive failure responded to rest and digitalis therapy, and he was discharged in fairly good condition on November 29, only to be readmitted 16 days later with nausea and vomiting, slight mental confusion and dizziness. Spinal-fluid examination revealed a total protein of 60 mg. per 100 cc. but was otherwise negative. The blood nonprotein nitrogen was 51 mg. per 100 cc., and the urinary sediment showed 20 to 30 white cells per high-power field. The total protein was 5.5 gm. per 100 cc. He improved and was discharged on January 3, 1942, although the ankle edema continued.

The final admission occurred only 3 days after discharge, when the patient again complained of nausea and vomiting, drowsiness and headache. The urine contained innumerable white cells, and there was a large trace of albumin. Examination of the blood disclosed a red-cell count of 3,800,000, with a hemoglobin of 12.2 gm. per 100 cc., and a white-cell count of 10,400. An electrocardiogram revealed low T waves and small QRS complexes, suggesting myocardial damage.

The patient improved strikingly and was ready for discharge on February 5, when he suddenly developed marked dyspnea and cyanosis and collapsed. He died within 10 minutes.

Autopsy revealed a terminal massive pulmonary infarction. The right foot showed histologic changes similar to those previously found in the left foot but without evidence of infection. A partial loss of bone structure, with evidence of bone absorption was seen, with a loss of joint spaces.

DIFFERENTIAL DIAGNOSIS

It is believed that the bone destruction in these cases represents a trophic change resulting from diabetic neuropathy and is similar to the arthropathies that may result from neurosyphilis, syringomelia, nerve injuries and the neural form of leprosy. Since the neuropathic foot is painless, the patient continues to walk and hence to traumatize the softened bones, a deformed thickened foot resulting.

In view of the resemblance to the true Charcot joint of syphilis it is essential to distinguish the diabetic neuropathic foot from this condition. The differentiation is not always possible by x-ray examination alone.

The classic arthropathy of Charcot often begins as a sudden spontaneous swelling of the joint and is rarely preceded by injury or by pain. In the ninety-two joints in 70 patients reported by Key,[8] injury had preceded the joint lesion in only 3 cases. The enlargement is due not only to an accumulation of fluid within the joint but also to periarticular swelling, which at times extends from the ankle to the knee. As the swelling increases, a feeling of tension and a variable amount of dull, aching pain in the joints may keep the patient awake at night. This acute stage may last for a week but subsequently subsides, with disappearance of the pain, and is succeeded by the chronic stage, in which the swelling is confined to the region of the joints and the disintegration of the joint progresses so that function is more or less impaired. Destruction and disintegration of the capsule and ligaments of the joint result in abnormal mobility. The articular cartilage is eroded, and the underlying bone may be eroded, with consequent fractures. Proliferation of cartilage and bone may occur, and there is often much thickening of the synovial membrane.

In Key's series of 61 White and 9 Negro patients with Charcot joints, there were no cases in which the diagnosis of neurosyphilis could not be made from the physical and laboratory examinations. In approximately a third of the cases there were no premonitory symptoms, but in the remainder, various symptoms were present, including shooting pain, ataxia, bladder dysfunction, visceral crises, optical atrophy, disturbances of sensation in the lower extremities, Argyll–Robertson pupil, loss of deep reflexes in the lower extremities and a positive Romberg test. In 60 cases the blood Wassermann test was positive in 19 and negative in 41. In 30 cases the spinal-fluid Wassermann test was positive in 11 and negative in 19. Roentgenograms showed excess fluid in the joints and tissues, erosion of the weight-bearing surfaces, the production of new bone, pathologic fractures, loose bodies in the joints and, most important of all, diffuse sclerosis.

The most striking differences between the true Charcot joint and diabetic neuropathic feet are the acute onset of fluid in the joint and the swelling of the extremity that may occur in the Charcot joint; the presence of pain in the Charcot joint during the acute stage; the frequent occurrence of new bone formation in the Charcot joint and the rarity of bone formation in diabetic neuropathic feet; the syphilitic sclerosis of the bone in areas near the involved joint; the almost constant occurrence of other symptoms, signs and laboratory evidence of syphilis in patients with Charcot joints; and the relative infrequency of Charcot joints in the feet.

In this group of cases of diabetic neuropathic feet, there was no clinical evidence of syphilis, and the 2 patients with positive blood Wassermann reactions had negative spinal-fluid findings.

The possibility of ischemic changes secondary to arteriosclerosis was considered, but in 14 of the 17 cases the pulsations in the dorsalis pedis arteries were easily felt and there was no evidence of impaired circulation. In the remaining cases, the collateral circulation was poor in 1 and good in 2. These findings, as well as the rarity of the condition as compared with the marked frequency of extreme peripheral arteriosclerosis in diabetes of long duration, make the possibility that ischemic changes play an etiologic role extremely remote.

The findings of other evidences of diabetic neuropathy in 14 of the 17 cases, the fact that other nerve lesions produce similar bone changes and the trophic nature of the lesion all suggest that the arthropathy is a manifestation of diabetic neuropathy.

Prognosis

None of the 17 cases showed any tendency to improve, and in most destruction gradually progressed. No treatment proved efficacious, but orthopedic appliances were used in an effort to relieve weight bearing and to avoid further deformity.

Summary

Seventeen cases of neuropathic foot lesions are reported. All had destruction of the tarsal or metatarsal bones that was roentgenologically similar to that observed in Charcot joints.

Evidence is presented that this bone lesion is trophic in origin and is a manifestation of diabetic neuropathy.

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MEDICAL PROGRESS

SYNTHETIC PLASTIC MATERIALS IN SURGERY (Concluded)*

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POLYETHYLENE

It has been known for many years that ethylene could be polymerized, but until 1936, when a new process involving high pressures was devised in England, only liquid and semiliquid polymers were obtained. Polyethylene was first employed experimentally in the United States in 1941.[57] The commercial use of polyethylene began here in 1943, when it was first produced in quantity.[1]

Ethylene has a simple chemical structure, and polyethylene, which is a polymer of ethylene, is —theoretically, at least — the simplest structure in which a chain polymer can exist. It consists of carbon atoms joined in a chain, each one carrying two atoms of hydrogen. These chains, according to Bailey,[58] range in length from 200 to 1000 or more units.

Polyethylene (also called "Polythene") is a tough thermoplastic resin that has a slightly cloudy appearance. It is flexible, resistant to water and most other solvents and chemically inert. It maintains its toughness over a wide range of temperatures. None of its characteristics change within the extent of human body temperatures. It is tasteless and odorless. It is light, with a specific gravity of 0.92–0.95. By a method known to the plastics industry as extrusion, the material can be formed into rods, tubes, sheets or films. In the process of extrusion polyethylene is supplied in bulk form to a cylinder. Under pressure and heat within the cylinder, the final product is extruded through an aperture in the desired form (Fig. 1).

One of the most desirable qualities of pure polyethylene from the point of view of use in the body is its flexibility without the addition of a plasticizer. On theoretical grounds because of its chemical inertness, simple chemical structure, resistance to water and pure state, this material should be well tolerated by tissues.

Polyethylene has found little place in medicine and surgery to date, but its flexibility, transparency and toughness and the facility with which it can be made into any size of tube or any thickness of film suggest multiple uses in the field of surgery.

Several possible drawbacks to the surgical applications of polyethylene should be mentioned. Since it is widely employed in industry because of its electric-insulating characteristics, manufacturers sometimes further enhance these properties by the addition of other chemical substances, known as antioxidants. Because one rarely knows what the added substances are, they must be considered harmful to the body unless proved otherwise. In obtaining this material, *pure* polyethylene should be specified. Manufacturers also state that polyethylene is occasionally extruded through a machine that has previously been used to extrude another substance containing a plasticizer or another chemical compound. It is apparently difficult to free the extruding apparatus completely of these substances, and for commercial use this is rarely necessary. Consequently, if this material is to be employed in surgical procedures, it is advisable to test small portions in experimental animals to be certain that it does not contain added chemicals irritating to the body. The material might, if found useful in a variety of surgical procedures, be dispensed by commercial medical-supply houses, which could take the responsibility of supplying a pure product.¶

Polyethylene will not tolerate sterilization by autoclaving, but it can be sterilized by boiling. It tends to retain the curve or shape in which it is placed during the process of boiling. Chemical sterilization by immersion in a 1:1000 solution of Zephiran for eighteen hours has been found satisfactory provided care is taken to see that the solution reaches the lumen of the tube and that the plastic, which is lighter than water, is kept completely in the solution and not floating on the surface.

Meyers[59] described a procedure of inserting a piece of small-caliber polyethylene (Med-O-Seal) tubing into a vein through a needle. This has provided a satisfactory method of giving repeated or constant intravenous injection through the same tube over prolonged periods without immobilizing the arm or leg. If intermittent injections are required, the tube is filled with physiologic saline solution at the completion of each injection, and the open end is plugged. Clotting does not take place within the tubing by this method, which Meyers used in 9 cases, in 2 of which he left the intravenous

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¶Polyethylene is now furnished by A. C. Balfour Associates, Englewood, New Jersey, as "Med-O-Seal."

tube in place four and five days, respectively. There was no noticeable tissue reaction to the tube.

Poppe and de Oliveira[60] report that Polythene cellophane produced a marked fibrous reaction when wrapped around the aorta in experimental animals. This film caused more reaction than a commercial cellophane, which in the experiments caused little reaction. These workers used Polythene film to wrap around a syphilitic aneurysm to cause thickening of the wall and obliteration of the aneurysmal sac. The use of the same material in aneurysms in 3 other cases and in a recurrent patent ductus arteriosus was mentioned, but none of the cases had been followed for a sufficiently long period to justify any conclusions. The experimental results of these workers are somewhat contrary to those of others reviewed below, particularly on the response to cellophane. They refer to Polythene cellophane or film, which in all likelihood was not pure polyethylene.

Ingraham, Alexander and Matson[61] performed animal experiments to determine the reaction of cerebral tissue to polyethylene. Sections of pure polyethylene tubing of small diameter were buried in the cerebral cortex of cats, dogs, monkeys and rabbits. The animals were sacrificed at intervals of two to ninety days, and the cortex containing the polyethylene was submitted for histologic study. The amount of reaction to this plastic was slight, and the tubing was surrounded only by a thin fibrous tissue layer. Emphasis was placed on the importance of obtaining absolutely pure polyethylene for surgical use. A variety of products supplied to industrial concerns under the name of polyethylene and Polythene contain chemicals other than the pure polymer. These are in general irritating to human tissue and should not be employed. In brief, these studies indicate that pure polyethylene is well tolerated by the body, with a reaction similar to that following the use of methyl methacrylate.

Preliminary studies carried out to determine whether polyethylene had any inactivating effect on penicillin showed no significant diminution in the effectiveness of the drug after contact with sections of the tubing for twenty-four hours. Narat and Cipolla[53] and Huelsebusch et al.[62] reported a drastic reduction in penicillin activity after contact with certain plasticized forms of synthetic tubing, including Tygon and White Surgical Koroseal. None of the materials tested had any effect on streptomycin.

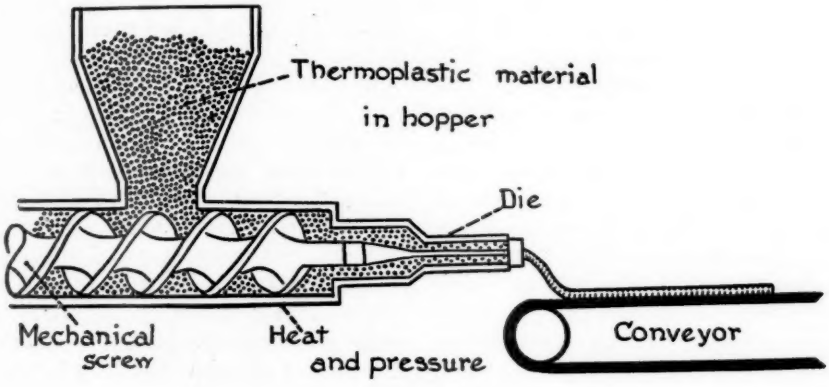

FIGURE 1.

CELLULOSE PLASTICS

Cellophane

The cellulose plastics were among the first used in industry. In 1869 Hyatt laid the foundation for the modern plastics industry by mixing cellulose nitrate with camphor to form a plastic material. This product is at present called "celluloid" or "Pyralin." Many chemical modifications of this substance were subsequently developed to form other plastic materials with desirable qualities. Cellulose acetate, a compound that is less inflammable, more durable and more easily molded than cellulose nitrate, is an example. Plasticizers are necessary to make these materials pliable, tough and durable.

One of the most important cellulose plastics is that known as regenerated cellulose, commercially called "cellophane." The chemical composition of the finished product is similar to that of the original cellulose from which it is derived. A complicated series of chemical reactions is necessary to produce this product, but in general the cellulose obtained from cotton or wood reacts with caustic soda and carbon disulfide to form cellulose xanthate, which on immersion in an acid bath is converted into regenerated cellulose. For many of the commercial uses of cellophane, impermeability to water is desirable. This is made possible by surfacing it with

a thin film of cellulose nitrate lacquer. Cellophane is formed in thin transparent sheets that are used for many purposes, prominent among which is the wrapping of packages of cigarettes.

Cellophane, with its smooth surface, pliability, toughness and transparency, has attracted the attention of many surgeons. Its properties invite its use in the human body as a covering or sheath where the normal coverings are lost.

Perhaps nowhere in the medical literature are there sharper contradictions regarding the reaction of a given material in the body than in the articles on cellophane. Some authors have maintained that it causes little or no reaction, whereas others have found that it incites an intense tissue reaction. One of the inherent difficulties has been the negligence of some of those who have reported on the use of cellophane to specify exactly what type they used. There are several different products, some treated with other chemicals to make them impervious to water. Probably many workers who have used these products with conflicting results have employed dissimilar chemical materials.

Another difficulty arising from the use of cellophane in surgery is the inaccessibility of information regarding plastic products from the manufacturers themselves. Chemicals may be used to treat plastics that are considered trade secrets by the industrial concerns that produce them. In general, the reports that cellophane is well tolerated by the body have been based on a few clinical trials unsupported by experimental work or histologic studies of tissues. The more careful studies of cellophane have shown it to incite such a foreign-body response that this particular quality has been used in unusual circumstances when intense scarring is desired.

Wheeldon[63] used cellophane that he designated "No. 300, moisture-proof, transparent film, 0.00088 inches thick." He performed a hip and a knee arthroplasty in which this material was employed as an interposition membrane, and the substance was also used in a tendon operation as a sheath. All the patients were reported to have benefited by the operations, and Wheeldon considered cellophane reactionless. No tissue-reaction studies were reported.

In like manner, McKeever[64] used No. 300 cellophane in 4 cases as an interposition membrane in synovectomy and considered it satisfactory. Harley and Breck[65] employed cellophane from cigarette packages in joint and tendon operations. They sterilized the material by boiling for twenty minutes and later "wiped off the waterproofing material." The patients were followed for only a few weeks and were reported as much improved by the operations.

Donati,[66] in Italy, used a commercial cellophane to replace the dura in a series of animal experiments. He reported that the brain showed no unusual reaction and that no adhesions were formed between the cerebral cortex and the material. The exact type of cellophane employed was not recorded, and there was no mention of its use in human patients.

In the Russian literature, Christyakov[67] recommended the utilization of cellophane as a protective covering over open or infected wounds. In the same communication, cellophane was reported to be satisfactory as a sheath around the anastomotic site in peripheral-nerve sutures. It had been used in 9 cases, as well as in 2 tendon operations. In the nerve anastomoses in 2 cases and in both the tendon cases, it was subsequently necessary to remove the cellophane, presumably because of infection.

In addition to the papers mentioned above, Poppe and de Oliviera[60] recently published an article describing experimental attempts at occlusion of vessels with various plastic materials. They reported the use of "No. 300 P.N.T. 71" and "No. 300 P.T. 62" cellophanes, which, they stated, are cellulose hydrate, nonmoisture proof and insoluble in water and dilute acids. They were said to produce little reaction when wrapped around the aorta of an experimental animal. No other mention was made of the type of reaction and no photomicrographs were shown, but the efficacy of cellophane in producing scar around a major artery was less than that of other materials used, including Polythene film.

In sharp contrast to the reports of authors who consider cellophane well tolerated by the body is a series of papers, most of them the accounts of careful experimental, clinical and histologic studies, condemning the material as an irritating foreign body or recommending it for use in tissue because of its ability to stimulate the formation of scar tissue. Indeed, as a result of work reported by Page,[68, 69] Graef and Page[70] and Dunihue,[71] the term "cellophane perinephritis" has been coined. This describes a type of dense scar tissue that forms around a kidney after a piece of du Pont P. T. 300 cellophane has been wrapped around it. This is a reliable method of producing experimental hypertension in animals. It causes an intense inflammatory reaction, with the attraction of many polymorphonuclear leukocytes followed by continuous fibroblastic activity and deposit of collagen. The cellophane does not disappear, and the response lasts as long as there are cells and vascular channels around the cellophane to permit reaction. This type of reaction of tissue to the material has also been found by Bailey and Ford,[51] who buried cellophane in the abdominal wall of guinea pigs and studied histologic sections of the tissue removed at various intervals.

Following the work of Page,[68, 69] Pearse[72, 73] studied the experimental occlusion of large arteries in animals by the use of du Pont P.T. 300 cellophane. In several animals complete closure of the aorta was obtained by this method. Pearse observed that this material was an extreme tissue irritant, since an in-

tense reaction occurred consisting in a collection of gelatinous or purulent fluid around which the fibrous tissue contained phagocytic mononuclear cells. A dense scar-tissue band was formed around the arteries wrapped with cellophane.

Gross,[74] in several of his early cases, wrapped du Pont P.T. 300 cellophane around the patent ductus arteriosus after it had been ligated. He found that the material aided in maintaining occlusion of the patent ductus arteriosus. More recently, he has found its use unnecessary, since he has been able successfully to divide and suture the ductus in the majority of the cases. The use of cellophane for this purpose has also been reported by Harper and Robinson,[75] and Harrison and Chandy[76] have employed it to occlude a subclavian aneurysm.

One can only conclude that cellophane is a strong tissue irritant and a potent stimulator of scar formation. There may be, and probably are, certain types of cellophane that are less irritating than others, but all experimental and clinical work that has been accompanied by adequate histologic studies confirms the conclusion that the material is irritating in the body. Its use, therefore, should be limited to the laboratory or to clinical cases in which a localized layer of scar tissue is desirable for therapeutic reasons.

Celluloid

Closely allied to cellophane chemically is another cellulose derivative, cellulose nitrate, mentioned above. This is better known by its trade name of "celluloid." As a general rule, camphor is used as a plasticizer for cellulose nitrate to produce the finished product.

For twenty years after World War I, sporadic reports of the use of celluloid as a material to fill skull defects appeared. An adequate review of this subject has been made by Grant and Norcross,[77] who found the material unsatisfactory in their own small series. In 1 case the celluloid plate was removed because of postoperative headaches. It was found to be enclosed in a sac formed by the pericranium and adherent to both pericranium and dura. The authors stated that the membrane was "several millimeters thick and was intimately connected with the dura, from which it was peeled off in layers until healthy dura was reached."

Ney[78] reported the use of celluloid in cranioplasty in 300 cases, with satisfactory results. He stated that there were infections in only 5 cases, although in all cases drains were left in the wounds for forty-eight hours and in most cases fluid continued to form over the plates for days or weeks. There were no histologic studies in this series, and there was no mention of a long-term follow-up study in any large percentage of the cases.

Woolf and Walker[11] reviewed the subject of cranioplasty and concluded that celluloid causes a moderate tissue reaction but that many such plates have remained in place for long periods. They stated that the material became brittle and friable after prolonged periods in the body. In view of the more recently developed alloplastic grafts that have proved easier to handle and are better tolerated by the body than celluloid, there seems little need for its use in cranioplasty.

Miscellaneous Plastics

In addition to the plastics described above as attaining relatively wide fields of usefulness in surgery, isolated reports of studies with other materials are found in the literature. In general, such reports illustrate the clinical use of plastics that seem to have desirable physical properties, without well controlled experimental or follow-up studies. Smith-Petersen[79] used a bakelite mold as a hip cup in an arthroplasty. The patient was reported as benefited when last seen two years after the operation. Bakelite is one of the organic synthetic resins of the phenol-formaldehyde group; so far as can be determined, no study of the response of tissue to such compounds has been made.

Baker[80] reported a new type of plastic hip cup for arthroplasty but did not mention the type of plastic used. He was primarily concerned with the form that the cup should assume in relation to the head of the femur.

Bellas[81] described histologic studies of a suture material called "Plastigut," which he described as a polymerized condensation product of aliphatic and aromatic alcohols with short-chain aliphatic aldehydes. The material was further described as a nonreacting, nonabsorbable, noncapillary suture that was satisfactory in surgical procedures. The histologic sections displayed showed little tissue reaction to the Plastigut.

Blaine[82] made various plastic materials out of casein, fibrin and other protein products. These plastics were formalized for varying periods. They were buried in the long bones of rabbits and studied at intervals. The protein plastics were all completely absorbed, the rate of absorption being inversely proportional to the degree of formalization. They maintained strength for only three or four weeks. Blaine noted that the breakdown of the proteins was probably "responsible for the heavy cellular infiltration commonly noted at an intermediate stage at the margin of the softened plastic." Nevertheless, he considered these plastics well tolerated. He did not believe that such products as he used were suitable for use in human subjects.

To illustrate the difficulty occasionally encountered in carefully delineating the field of plastics, reference should be made to methyl cellulose, which is manufactured industrially as a mucilage and is soluble in cold water, giving a water-clear, viscous colloidal solution. It has been described as a methyl ester of cellulose and consists of a long chain of dextrose molecules. Hueper, Martin and Thompson[83]

recommended it for use as a plasma substitute in place of acacia. It was fairly well tolerated in animals when given as a 2 per cent solution intravenously, but it has the disadvantage of being stored in the liver, spleen and kidneys. Presumably, since the advent of readily available plasma during and following World War II, it will not be widely used in blood-replacement therapy.

Discussion

A factual review of the application of industrial plastics in the field of surgery has been presented. The tremendous variation in plastic materials, with the production of literally thousands of different types, is at first sight confusing, but on closer study it is evident that for the selection of materials to be buried in human tissues, certain definite criteria are necessary. Primarily, such criteria forbid the use of any plastic that can do harm to the body either by toxicity or by irritating properties causing excessive scar-tissue formation. There are certain exceptions to this rule in the use of materials to cause the formation of a localized area of scar tissue, as in the obliteration of a patent ductus arteriosus or the surgical treatment of aneurysms, but the exceptions are few and well known.

Choosing industrial plastics for use in surgery is therefore much more than a selection of certain materials that possess desirable physical properties. In general, plasticizers incorporated within plastics are not well tolerated by the body. The exclusion of all plastics containing plasticizers greatly narrows the field of selection; when the field has been further delineated by the requirements imposed by necessary physical properties for specific uses, a small number of plastic materials remain. From the review presented above, it is all too obvious that frequent clinical use of plastics has been made without any controlled studies. Consequently, many publications on the employment of plastics in surgery are merely the reports of the isolated use of some plastic material in clinical surgery.

In an attempt to be exact in the study of plastics, a difficulty is encountered — namely, the possession of certain commercial secrets by industrial concerns. As a result, in experimental work with plastics it is sometimes impossible to obtain information regarding the chemical make-up of the compounds used. Furthermore, the industrial utilization of plastics does not require the same purity as the surgical use of the same materials. If an apparatus employed to produce a plastic tubing, for example, has been previously used to produce some other material, it may contain minute quantities of irritating chemicals of no significance to industry but of potential harm in surgical procedures. This factor must be taken into consideration, particularly when plastic tubing such as polyethylene is employed. The dispensing of a standard product of nylon sutures by medical-supply houses minimizes the importance of this point for such material. Methyl methacrylate can be easily polymerized as a pure chemical product with little danger of added chemical impurities. Cellophane is in no sense of the word a pure product, and in view of the fact that it should be used only where localized scar tissue is desired, the problem resolves itself into a search by the investigator for commercial brands of the product that are sufficiently irritating to the body for the desired use.

There are many obvious discrepancies in the medical literature dealing with plastics — disagreements that do not appear reconcilable. In the main, these discrepancies are based on the failure of some investigators to specify exactly the plastic product used in the work they have reported. In some instances it has been difficult, because of commercial secrets, to obtain detailed information, and in others it appears that impurities, of which the investigator was unaware, were included in the materials. Whatever the reasoning behind the reporting of the surgical use of plastics without exact knowledge of the plastic, the practice of choosing such materials for clinical trial because of their desirable physical properties alone should be abandoned. Sufficient knowledge regarding plastics is now available to enable one to choose a material that is well tolerated as well as one that possesses desirable physical properties. If other materials are needed, or if promising new plastics appear, their clinical use should be preceded by adequate experimental study.

Three plastic materials have been found to be well tolerated by the body, and in aggregate they offer an imposing list of desirable physical properties from which a selection can be made for surgical use. Methyl methacrylate (Lucite, Plexiglas), a pure polymer that is hard, transparent, and easily cast into desired forms, can be used for cranioplasty, for implants in various parts of the body and in the form of rigid tubes. Nylon, in the form of a filament, is at present employed only as a suture material. Polyethylene (Polythene) is a polymer of simple chemical structure that is pliable, soft and relatively transparent. Its primary value has been in the form of tubing.

Summary

A review of the medical literature regarding industrial plastics is presented. Three plastic materials are well tolerated by the body: methyl methacrylate (Lucite, Plexiglas), nylon sutures and polyethylene (Polythene).

Cellophane is in general a severe tissue irritant, of use in surgery only to incite scar tissue.

A variety of other plastic materials have received sporadic clinical trial but are not recommended.

Adequate experimental trial should precede the clinical use of any untested plastic material in surgery.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33111

Presentation of Case

A thirty-seven-year-old Swedish asbestos worker entered the hospital because of cough and chest pain.

Two and a half years before admission the patient had developed a cough, nasal congestion, nasal discharge, fever and shortness of breath that had persisted one week and had been followed by a dull, aching pleuritic pain along the left costal margin. He was hospitalized for a week and then rested at home for four months. In the hospital about 1000 cc. of fluid was removed from the left side of the chest. Subsequently, he returned to work and felt well except for a morning cough productive of small amounts of odorless white sputum. Occasional chest pain and exertional dyspnea were also noted. A year and a half later there was an insidious onset of weakness and fatigability and a gradual loss of 25 pounds in weight. Three months before entry the pleuritic pains became persistent, and the weakness and dyspnea severe, and the patient slept propped on two pillows. Repeated sputum smears were negative for tubercle bacilli.

The patient's work consisted in cutting asbestos insulating board; he denied exposure to undue amounts of dust. There was no history of exposure to tuberculosis.

Physical examination revealed the patient to be orthopneic and breathing rapidly at a rate of 30 per minute, with a dry, hacking cough and clubbed fingers. There was a slight, shotty, generalized lymphadenopathy. Respiratory expansion on the left was diminished, as were tactile and vocal fremitus and breath sounds. On the right there were increased bronchovesicular breath sounds and scattered dry rales. The heart and mediastinum were shifted to the right, and the apical beat was maximal in the right midclavicular line. There was a ticktack rhythm with a rate of 110, and a pulsus paradoxicus. The abdomen was normal.

The temperature was 100°F. The blood pressure was 128 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 4,900,000 and a white-cell count of 12,200, with 77 per cent neutrophils, 16 per cent lymphocytes and 7 per cent monocytes. The urine and stools were normal. X-ray examination showed numerous discrete areas of increased density scattered over the right lung; pressing on the lower trachea and left main bronchus and deviating them to the right was a large mass measuring 11 cm. in diameter (Fig. 1). A small amount of aerated lung was seen at the periphery of the mass. There was either fluid or, more probably, dense pleural thickening and collapsed lung between the mass and the lateral costal margin. The left lower-lung field was almost completely opaque.

In the hospital the patient's condition became steadily worse. Further x-ray studies showed displacement of the esophagus to the right (Fig. 2), extensive periosteal new bone formation of the left upper ribs, slight displacement of the stomach to

the left, enlargement of the spleen and the suggestion of a retroperitoneal mass rotating the left kidney. Three attempted thoracenteses failed to encounter fluid, although the needle was inserted to a depth of 5 cm. No acid-fast organisms were found in the sputum. Tuberculin tests were negative in a 1:1000 dilution. The patient became extremely weak and dyspneic and perspired constantly. He died on the thirty-seventh hospital day.

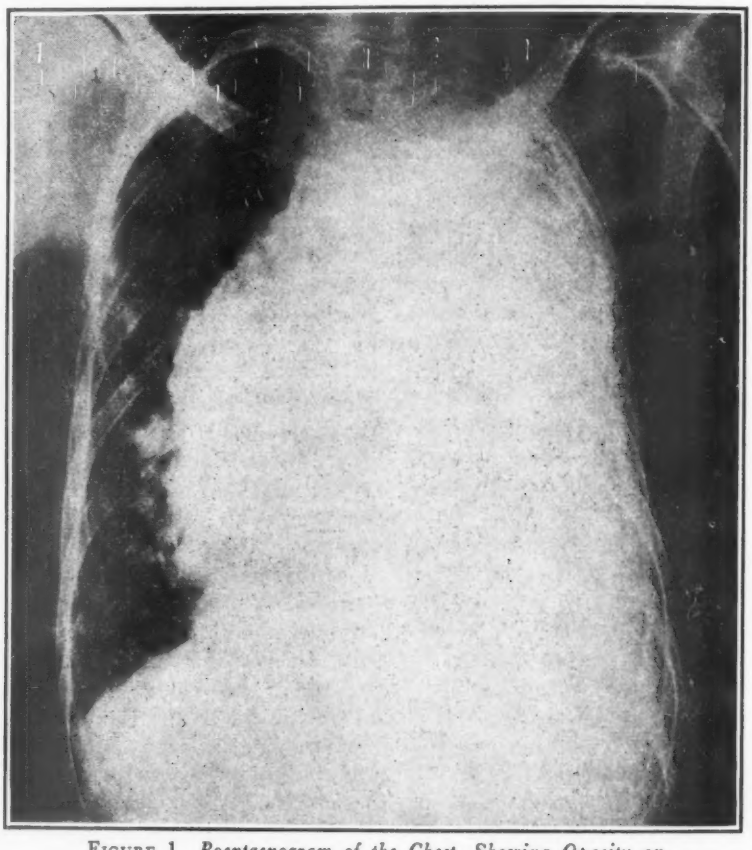

FIGURE 1. *Roentgenogram of the Chest, Showing Opacity on the Left and Multiple Nodules in the Right Lung.*

DIFFERENTIAL DIAGNOSIS

DR. DONALD S. KING: This seems to be the old problem of a tumor in the lung with a decision to be made regarding the kind of tumor. As in most cases, the decision will be based largely on the x-ray appearance.

One should comment first on the occupation. This man worked with asbestos, cutting insulating board. Exposure to asbestos causes lung changes but never, in my experience, to the extent that was present in this case. I believe that asbestosis was not a factor in the illness and that, if present, it was of secondary importance.

The next question concerns tuberculosis. The onset of the disease was two and a half years before the final hospital admission, with fever for a week. About 1000 cc. of fluid was removed, following which the patient was discharged from the hospital. He then rested at home for four months, returned to work and remained in good condition for a year. This could have been pleurisy with effusion, perhaps tuberculous. Many sputum examinations, however, showed no tubercle bacilli, and shortly before death a tuberculin skin test was negative in a 1:1000 dilution. In any event, the evidence for tuberculosis does not seem sufficient to justify that diagnosis in addition to what I believe was a tumor. My diagnosis is tumor, with fluid that was secondary to the tumor and not due to tuberculosis or other infection.

The x-ray films present a different picture on each side of the chest. On the right side there are many nodules, which are better shown in some films than others. In my experience, rounded nodular shadows of this sort have always been caused by metastatic tumor, either from some spot elsewhere in the lung or from some place outside the chest. If the tumor was metastatic from outside the lung, it could have been from above the clavicles or below the diaphragm, or there could have been metastases from a primary bronchiogenic cancer in

the left lung or from a mediastinal tumor. I should like to ask Dr. Schatzki whether he has ever seen rounded shadows of this size and density that were not due to tumor.

DR. RICHARD SCHATZKI: Yes.

DR. KING: I stand corrected on that point.

DR. SCHATZKI: That does not mean that this was not a tumor.

DR. KING: I have never seen rounded shadows of this size and distribution with silicosis, tuberculosis or in fact anything, and I therefore believe that the process in the right lung was definitely a metastatic tumor. The x-ray film of the left side of the chest shows a large, round mass displacing the trachea and the left main bronchus to the right. Is the tumor in the lung itself or in the mediastinum?

DR. SCHATZKI: The same mass is visible on this film in the same position. I do not believe that one should try to delineate the exact outline of the tumor when so little air is present. Other criteria should be used to demonstrate the mass. The only air left in the left lung is the small amount seen in the left upper lung. The films do not show what is going on lower down.

DR. KING: So you will not help regarding the position of the tumor — that is, whether it is in the lung or outside the lung?

DR. SCHATZKI: I think that I could help if I was allowed to.

DR. KING: I think that it would be all right; how about it, Dr. Castleman?

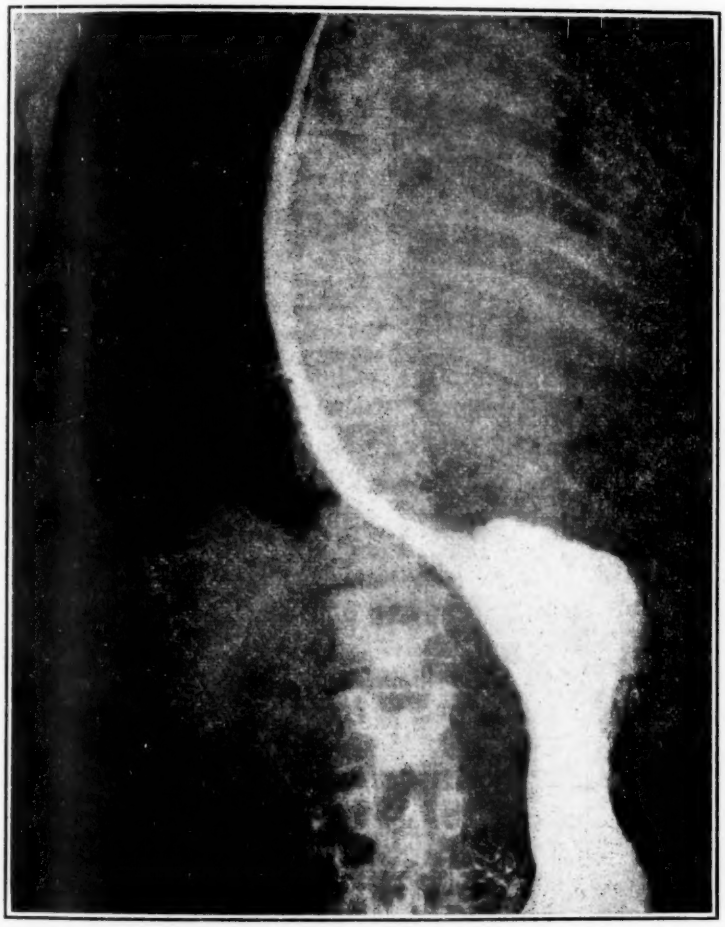

FIGURE 2. *Roentgenogram of the Chest and Abdomen following a Barium Swallow, Showing Displacement of the Esophagus and Stomach by a Mass in the Left Side of the Chest.*

DR. BENJAMIN CASTLEMAN: By all means.

DR. KING: I need a great deal of help.

DR. SCHATZKI: There is some definite evidence of a large mass outside the lung. The first indication is the position of the esophagus, which is displaced far to the right side by a mass. This mass has a diameter much larger than the mass in the upper-lung field, and therefore it cannot be a tumor in the lung. The second point is the position of the fundus of the stomach, which is pushed downward in contrast to what one would expect with a lung tumor

that has produced collapse. Thirdly, the ribs, if anything, are spaced farther apart than on the normal side, which is again unusual for a lung that has collapsed.

DR. KING: I should have committed myself before I asked that question, but I agree with your conclusions. I cannot be sure that this was not a bronchiogenic carcinoma of the left upper lobe, but my opinion is against that diagnosis. There was also involvement in the left lower lobe. I suppose that this also may have been a tumor. Do you want to commit yourself on that, Dr. Schatzki?

DR. SCHATZKI: I think that I know the answer. It is obvious, as I have said, that there was something outside the lung; otherwise, the stomach would not have been displaced or the ribs separated.

DR. KING: Do you think that it was a tumor or fluid?

DR. SCHATZKI: I believe that it was a tumor.

DR. KING: That is what I believe.

Let us go down to the abdomen. Was the spleen enlarged or was it displaced downward? I should like to omit the spleen if I may.

DR. SCHATZKI: So far as I am concerned, it may be excluded.

DR. KING: Was the stomach involved?

DR. SCHATZKI: There is no evidence of involvement of the stomach. It was displaced, but this was due to the low position of the left leaf of the diaphragm.

DR. KING: Was the liver enlarged? And was the displacement of the stomach to the left due to such enlargement?

DR. SCHATZKI: The liver was not enlarged so far as I can tell.

DR. KING: This is an intravenous pyelogram showing a retroperitoneal mass rotating the left kidney.

DR. SCHATZKI: Both kidneys are low in position, and I am wondering if what we see is not again due to the low position of the diaphragm.

DR. KING: You do not see the retroperitoneal mass?

DR. SCHATZKI: Not that I can be sure of. I do not see the outline of the kidneys so well as I should like to. The upper pole of the right kidney is clearly seen, but the upper pole of the left kidney is not.

DR. KING: I suppose that you have helped all you can. Do you want to say anything more?

DR. SCHATZKI: Yes; there are some rib changes.

DR. KING: You mean the periosteal changes in the rib? I have seen such changes only with pus. Have you seen periosteal changes with large tumor masses?

DR. SCHATZKI: We have seen them in patients who did not have empyema but who had a chronic nonspecific process in the lung.

DR. KING: The films show the periosteal changes clearly, and I am inclined to agree.

Actually, we have no evidence of any source of tumor outside the chest, but the possibility of tumors in the pharynx and the thyroid gland should be mentioned because findings similar to those in this case follow metastases from malignant tumors in those areas. We are not justified, however, in making such a diagnosis with the evidence at hand. Below the diaphragm there is no indication of disease of the stomach, pancreas, liver or kidney. These films at first suggested that the testicle or the prostate was the primary source, or perhaps a so-called "hypernephroma." This is a fairly characteristic picture for metastases from the testicle or prostate, but we have no evidence to make that diagnosis. There does not seem to me to be any justifiable source for the tumor outside the chest, and we are back to the problem of what this tumor was.

Was it bronchiogenic or mediastinal? We have seen exactly this picture with teratomas of the mediastinum that have eventually broken loose. If it was a lung tumor I lean toward a bronchiogenic carcinoma with metastases to the right lung and possibly the retroperitoneal area. The findings were not quite consistent with those of bronchiogenic carcinoma because such tumors are usually not large enough to push the mediastinum to the other side unless a great deal of fluid is present. Also, the rib changes were more like those with a large tumor mass that had been pressing on that area for some time. The process had been going on for perhaps two and a half years. My diagnosis is a mediastinal tumor, probably a teratoma, with metastases to the right lung. I do not believe that the tumor was a lymphoma, although again that must always be considered. I doubt whether it was a bronchiogenic carcinoma with metastases.

DR. F. DENNETTE ADAMS: How do you exclude lymphoma?

DR. KING: I do not exclude it. I have not seen x-ray findings such as these with lymphoma, which usually causes more symptoms than this man had for two and a half years. The other conditions I have named seem likelier.

DR. ALFRED KRANES: Is it not unusual for fluid due to tumor to subside for so long a time?

DR. KING: Yes: that is one of the things against trying to explain the whole picture as tumor. I agree that subsidence of all symptoms for a year after the removal of 1000 cc. of fluid in a case of tumor is not usual. I wanted to make the diagnosis of tuberculosis, but I could not.

DR. CHARLES L. SHORT: I saw this patient on the ward, and I went through much the same line of reasoning as Dr. King has. From the history my impression was tuberculosis, but from the x-ray findings that certainly could not have been the primary diagnosis. I do not believe that most of us went so far as Dr. King in being willing to say that the tumor was primary in the chest. We thought of lymphoma and for that reason small

doses of x-ray therapy were given, without effect on the lesion. We were able to get a needle biopsy shortly before death. A mass developed above the left clavicle about 5 cm. in diameter, and we thought that there was also a mass in the epigastrium.

DR. KING: Such metastases would be against my diagnosis. A primary carcinoma of the lung would be likelier to metastasize to the neck, although lymphoma could do so.

CLINICAL DIAGNOSIS

Carcinoma of lung, probably metastatic.

DR. KING'S DIAGNOSIS

Mediastinal teratoma, with metastases to right lung.

ANATOMICAL DIAGNOSIS

Mesothelioma of pleura and pericardium, with metastases to right lung and retroperitoneal lymph nodes.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The left lung was completely encased on all sides by a thick, hard, somewhat

FIGURE 3. *Photograph of Coronal Section of the Left Lung, Showing Complete Encasement by the Pleural Tumor.*

shiny, fibrous tumor compressing the lung into a small fraction of its normal volume. In places this thickening of the pleura or tumor tissue involving the pleura measured as much as 8 cm. (Fig. 3). There were multiple tumor nodules in the right lung, but no involvement of the pleura. This was in sharp contrast to the left lung, which was free from any parenchymatous tumor nodules. The heart and pericardium together weighed 1100 gm. The heart itself was perfectly normal, the increase in weight being due to the tremendous thickening of the visceral pericardium, which measured as

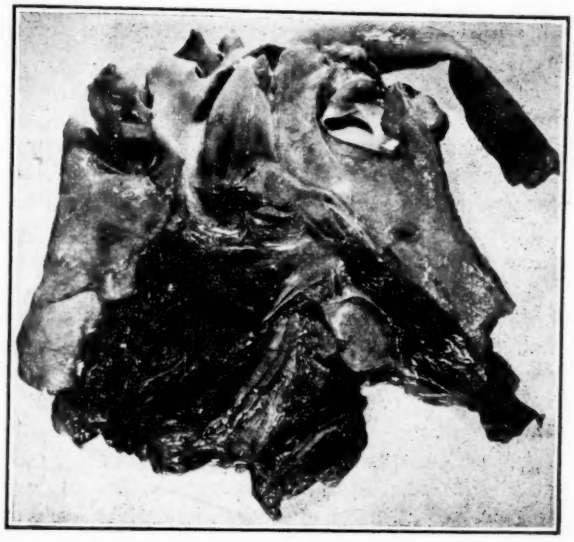

FIGURE 4. *Photograph of the Heart, Showing Neoplastic Involvement of the Visceral Pericardium.*

much as 3 or 4 cm. in thickness (Fig. 4). This gross picture of involvement of the pericardium and

FIGURE 5. *Photomicrograph of the Mesothelioma.*

pleura fits in with the diagnosis of mesothelioma. We examined the bronchi carefully throughout the left lung and found no evidence of tumor within a

bronchus, near a bronchus or in the lung itself. The nodules in the right lung were well circumscribed in the parenchyma away from the bronchi and were definitely metastatic. We were quite certain that we could rule out bronchiogenic or primary carcinoma of the lung. The bronchial lymph nodes contained no tumor. We searched every organ for a primary source, but we were unable to find any.

The histology of the tumor was typical of what has been described as a mesothelioma (Fig. 5). The cells in some areas were cuboidal and arranged around fibrous stalks giving a pseudopapillary pattern. In other areas the cells were large, irregular and closely packed. Some were multinucleated, and others seemed to be forming mucinous material.

A number of papers have been written to the effect that there is no such tumor as mesothelioma of the pleura, that the cells lining the pleura do not form tumors and that these tumors really arise from a small focus in the lung. We have held a similar opinion for a long time. This is perhaps the first case in which we believed that there was actually such a tumor. It certainly fits in with most of the cases of mesothelioma of the pleura that have been reported.*

DR. KING: I do not consider that it is fair to have given me a case with a diagnosis against which you, as pathologists, have been talking for twenty years. I could never make Dr. Mallory accept a diagnosis of mesothelioma of the pleura.

DR. CASTLEMAN: He has been sold on this one. The lesion in the abdomen was retroperitoneal tumor, but there was no tumor elsewhere.

DR. ADAMS: What was the large lesion in the left lung?

DR. CASTLEMAN: It was merely nodularity due to the pleural tumor.

*Klemperer, P., and Rabin, C. B. Primary neoplasms of pleura. *Arch. Path.* **11**:385-412, 1931.

CASE 33112

PRESENTATION OF CASE

A seventy-two-year-old Polish housewife entered the hospital in coma.

Eleven days before entry the patient had received a slight back injury in an automobile accident. A physician examined her at that time and found only slight spasm along the lumbar muscles. Three days later the physician was called again because the patient complained of slight bleeding supposedly from the vagina; he could find no evidence of bleeding. Six days before entry the patient began to have frequent episodes of abdominal cramps. These continued daily. Three days later the abdomen was distended, with marked tenderness and a mass in the right lower quadrant. The patient was taken to another hospital, where a plain film of the abdomen and a barium enema showed an abrupt, shelf-like obstruction in the lower sigmoid, with a markedly dilated large bowel, particularly on the right, and beginning small-bowel dilatation. Routine urine examinations were said to have been negative. There was a slight leukocytosis, and the blood sugar was 196 mg. per 100 cc. On the following day the patient appeared acutely ill. The abdomen was greatly distended, and the patient complained of abdominal pain. No organs or masses could be felt. The pulse was about 115. On the same day an emergency cecostomy was performed under a local anesthetic. There was an increased amount of clear, straw-colored fluid in the peritoneal cavity. The colon and cecum were greatly distended, and a large amount of fluid and gas was removed by trocar suction. A glass Mixter tube was fixed in place by sutures. Following the operation the patient was said to have improved for a while, but the abdominal symptoms subsequently reappeared. She was transferred to this hospital on the afternoon of the second postoperative day.

The patient was known to have hypertension. A sister had diabetes.

Physical examination revealed an obese, disoriented woman. The left border of the heart extended beyond the midclavicular line, but the heart sounds were normal. There were coarse rhonchi, which cleared on coughing, in both lower lobes. The abdomen was distended, tense and slightly tender. Peristalsis was limited to a few tinkles. The diaphragm was high on both sides but moved to percussion. The cecostomy appeared to be functioning well.

The temperature was 100°F., the pulse 120, and the respirations 30. The blood pressure was 110 systolic, 70 diastolic.

A Levine tube was passed immediately on entry, and 500 cc. of brownish fluid, as well as considerable gas, was aspirated from the stomach. The patient also received 600 cc. of 5 per cent dextrose in water and oxygen. During the night she became extremely disturbed, tore up the oxygen tent and pulled out the intravenous drip and stomach tubes. The cecostomy drained 1680 cc. of fluid, and 646 cc. of urine was passed on the first hospital day. On the morning of the second hospital day the distention appeared to be slightly less, and peristaltic tinkles were somewhat more frequent. The tongue was dry.

The temperature was 102°F., the pulse 130, and the respirations 30. The blood pressure was 100 systolic, 60 diastolic.

Examination of the blood showed a hemoglobin of 16.3 gm. per 100 cc., a hematocrit of 50 and a white-cell count of 9700, with 85 per cent neutrophils. The total protein was 8.5 gm. and the nonprotein nitrogen 100 mg. per 100 cc.; the carbon

dioxide content was 30.1 and the chloride 91 milliequiv. per liter. The prothrombin time was 18 seconds (normal, 14 seconds).

The urine was acid, had a specific gravity of 1.026 and gave a ++ test for albumin. It did not contain sugar or diacetic acid. The sediment showed many hyaline and some granular casts, as well as 6 white cells per high-power field. X-ray films of the chest and stomach showed the diaphragm to be high in position, and there were segmented areas of atelectasis in the left lower lobe. The stomach was greatly distended by gas. The small intestine contained a moderate amount of gas but was only slightly dilated. The colon was not distended, but the right side contained a large amount of fecal material.

During the day the patient gradually became drowsy. She was given 1500 cc. of 5 per cent dextrose in physiologic saline solution and 900 cc. of 5 per cent dextrose in water, and administration of 100,000 units of penicillin every three hours was begun. In the afternoon the chloride had fallen to 74 milliequiv. per liter. The patient was cold and clammy and appeared sicker, although the abdomen was softer and peristalsis was improved. The blood pressure was 160 systolic, 90 diastolic, and the pulse was strong. The cecostomy drainage was 475 cc. The urine output had fallen off, although the actual amount was not recorded.

On the third hospital day the patient seemed somewhat more alert. The abdomen was much softer, and peristalsis was fairly good. The heart sounds, however, were distant, with a ticktack rhythm. The hematocrit was 57. The protein was 8.5 gm., the nonprotein nitrogen 155 mg. and the blood sugar 200 mg. per 100 cc.; the chloride was 85 and the carbon dioxide 30.8 milliequiv. per liter. The patient was given 3000 cc. of 5 per cent dextrose in saline solution and started on 8 units of insulin. The cecostomy drainage was 230 cc.

On the fourth hospital day the temperature rose to 105°F., and the patient became incoherent and restless, with muscle twitching. The hematocrit was 56. The chloride was 92 and the potassium 2.5 milliequiv. per liter, the nonprotein nitrogen 150, the calcium 7.7 and the blood sugar 308 mg. per 100 cc. An electrocardiogram showed a sinoauricular tachycardia at a rate of 125. There were low T waves and moderate left-axis deviation. The chest leads showed a low T wave in Lead CF_4. The patient was given 20 cc. of calcium levulinate without any effect on the muscle twitching. She also received 500 cc. of 5 per cent dextrose in physiologic saline solution, 500 cc. of whole blood and 2500 cc. of 5 per cent glucose in half-strength physiologic saline solution. Nevertheless, she gradually relapsed into coma, and by evening the temperature had reached 106°F. She died on the fifth hospital day.

Differential Diagnosis

Dr. William W. Beckman: This case is a new experience for me because yesterday Dr. Castleman sent the clinical record of this patient to my office and said that I could read it. The record provided really only one datum that is not in the protocol. One gathered from a reading of the record — although it did not state definitely — that a Levine tube had been present in the stomach most of the time that the patient was in the hospital. There was constant drainage from the tube, although the amount is not stated.

Dr. John B. McKittrick: That is true.

Dr. Beckman: The point about this case that struck me when I first read the record was that the patient apparently had no abdominal pain until six days before entry. Five days before its onset she was examined by a physician who knew her language, — she did not speak English, — and there were no abdominal complaints. She had had a rather abrupt onset of abdominal cramps and apparently went rather rapidly into collapse. X-ray studies revealed obstruction of the sigmoid, which either had become acutely obstructed or, it seems even more probable to me, had perforated and caused peritonitis. I believe that, instead of actual obstruction from a carcinoma, paralytic ileus was present. In any event it is clear that the patient had a carcinoma. There is no question that cecostomy was the indicated step.

The patient was admitted in coma and was known to have an elevated blood sugar, which brings up the possibility of diabetes. Another thing I learned from the record was that there was practically no acetone in the urine. This fact and the carbon dioxide measurements are against diabetic acidosis as an explanation for the coma; indeed, the possibility of diabetic acidosis can scarcely be entertained. The patient probably had the type of acidosis associated with arteriosclerosis in old people, which does not, so far as I know, produce coma. She had diabetes. One cannot be certain, however, how severe the diabetes was because in the hospital she was given injections of glucose that may have contributed to the elevation of the blood sugar.

The significance of the urinary findings is difficult to evaluate. The urine was said to have been normal when the patient was in the outside hospital. She had only one specimen here, which showed casts and albumin and which probably represented a certain amount of kidney disease, probably so-called "vascular nephritis." How much this contributed to the elevated nonprotein nitrogen is difficult to evaluate, because extrarenal factors must be considered.

Another point that was not mentioned in the protocol or the record is that the patient apparently had a fairly adequate urinary output during most of the hospital stay. In spite of this there was

evidence of marked depletion of the extracellular fluids, on the basis of the marked hemoconcentration shown by the elevated total protein, hemoglobin and hematocrit. There was a low chloride, a low calcium and a low potassium. For some reason there is no mention of the sodium. There was an elevated carbon dioxide content. All these things together indicate that the patient had lost a great deal of fluid from the upper gastrointestinal tract rather than from the cecostomy and that she had an alkalosis as a result of the removal of hydrochloric acid from the stomach.

I suppose that I was given this case to discuss the therapy, but I have always believed that this kind of exercise, in which the case terminates at autopsy, is not a satisfactory way of evaluating therapy. If we were to base an evaluation on such cases we should have to conclude that penicillin was of no value, and that is not quite true. The patient was desperately ill when first seen at the other hospital, and I give credit to everyone for the restrained but expeditious way in which the illness was managed. Every effort was made to correct the various surgical, bacteriologic and chemical abnormalities that were present. A cecostomy was performed to relieve acute large-bowel obstruction. Penicillin was given for what I think was peritonitis. The patient was given sufficient replacement fluid, but with restraint. Another point in the clinical record is that she was seen by Dr. Allan M. Butler, who thought the low potassium represented serious difficulty and suggested the intravenous administration of potassium. There is no way of knowing from the record whether potassium was given.

DR. MCKITTRICK: Potassium was not given.

DR. BECKMAN: It is difficult to administer a significant amount of potassium by vein, for high serum concentrations affect the myocardium and produce ventricular fibrillation. Perhaps with the low value it would have been proper to give a small amount, but potassium must always be given in concentrations not exceeding 4 to 6 milliequiv. per liter — the normal value for serum.

DR. MCKITTRICK: I should like to say that Dr. Beckman is a good detective because he deduced all the omissions from the record with exact accuracy. The Levine tube was taken out forty-eight hours before death. His deduction regarding the electrolyte loss is correct, in that for practical purposes all the loss was from the Levine tube. The short history, so far as anyone could determine, is correct. The patient had symptoms for only six days prior to death; they consisted chiefly of abdominal cramps, which began suddenly.

The question of coma on entry is interesting. I did not believe that the patient was in coma. She was moderately irrational, although she did answer questions in her own language. If she was in coma I do not know what kind, but it certainly was not diabetic coma.

The only blood sugar determinations that indicated a disturbance in glucose metabolism were the ones taken before entry and the one taken at this hospital before intravenous therapy was given. The urinary output was fairly good throughout the hospital stay, with the exception of the last twelve to fourteen hours, when it was markedly diminished — in fact, practically nonexistent. The sodium determination was not done purposely; Dr. Butler, who was called in to see this patient, did not believe that it would help a great deal in planning the treatment. An electrocardiogram was taken in an effort to determine whether there was any evidence of a low potassium, but we could not get any assurance on that score. The report on the determination of potassium came back twenty-four hours later. Despite the low value, Dr. Butler, who was handling that aspect of the therapy, was not quite ready to give intravenous potassium.

My point of view in the treatment of this patient was one of timidity. She was seventy-two years old and had hypertension; she was admitted with a low blood pressure and was probably a senile diabetic patient, as Dr. Beckman has deduced. There was tenderness only over the sigmoid — a point that is not mentioned in either the record or the protocol. At one time we believed that we had induced a certain amount of pulmonary edema with the intravenous therapy. We were cautious about giving potassium, but it may have been needed. All along the line we trailed the patient physiologically; we never did catch up with her. On the night of admission I hesitated to give saline infusion. Whether she should have had saline or something else, I did not know. Peritonitis appeared to be present — I could not understand the small-bowel dilatation, the tremendous dilatation of the stomach or the ileus on any other basis. This was an extremely perplexing problem throughout. All of us see cases like this once in a while, and do not know how to handle them. This is a good case in point because obviously we did not handle the problem correctly. I think that the autopsy findings will either help in the deduction of what should have been done or add further confusion.

DR. VINCENT P. DOLE: The single reported urine specific gravity of 1.026 suggests that the renal function was adequate and that the limitation in renal performance was due to extrarenal circulatory disturbances. It is conceivable that with this infection there was subsequent intrinsic renal impairment. Toward the end the apparently adequate renal output may have been misleading if the kidneys had lost their capacity to concentrate.

DR. MCKITTRICK: Several urine analyses were made at the other hospital. Incidentally, I was the surgeon who did the cecostomy. There was an adequate specific gravity. Unfortunately, only one

determination was made here, but I think that it was everyone's impression who followed this patient that the renal function was reasonably good until terminally, when the urinary output suddenly dropped and the patient excreted practically no urine.

Clinical Diagnoses

Carcinoma of sigmoid, with perforation.
General peritonitis.

Dr. Beckman's Diagnoses

Carcinoma of sigmoid.
Intestinal obstruction (? paralytic ileus or mechanical).
Peritonitis.
Mild vascular nephritis.
Diabetes mellitus.
Severe dehydration.
Alkalosis.

Anatomical Diagnoses

Colloid carcinoma of sigmoid, with perforation and localized peritonitis.
(Electrolytic imbalance, with renal insufficiency.)

Pathological Discussion

Dr. Tracy B. Mallory: Autopsy showed some of the obvious things that were predicted. There was a carcinoma of the sigmoid, and there was also extensive diverticulosis of the same area. The large bowel was full of feces despite the cecostomy. The peritoneal cavity showed fresh, rather loose adhesions that were probably due to the cecostomy operation a few days earlier. There was no generalized peritonitis. The carcinoma and the area of bowel immediately around it were necrotic and pulled apart in the prosector's hands as he was dissecting it. Although there was a localized sepsis, there was no general peritonitis.

I think that the major question of interest concerns the kidneys in that there seemed to be so much functional evidence of renal insufficiency — they showed practically nothing. The proximal convoluted tubules were swollen, and occasional loops of tubules revealed albuminous degeneration. It was the extremely mild nephrosis that Fahr* would have described as Grade I nephrosis when he wrote his monograph. I gather from the autopsy findings that the nitrogen retention and other changes were, as Dr. Dole suggested, prerenal rather than renal. I do not believe that the renal lesions can even remotely explain the functional findings.

Dr. Beckman: I should like to emphasize again that I still believe that the fluid administration was carried out with the proper restraint. I do not believe that one can stress the point too strongly that in a person with high blood pressure and hypertensive heart disease the administration of intravenous fluid and transfusions are apt to cause pulmonary edema. This is due to the development of acute left ventricular failure, with resultant congestion of the lungs.

Dr. Leonard P. Eliel: What do you think about the administration of 1.8 per cent of physiologic saline solution in a case of this sort to make up the salt deficit and not give too much fluid?

Dr. Beckman: I suppose that that would be wiser. I have not had any experience with such therapy.

Dr. McKittrick: I had a rather uncomfortable experience in a similar problem with a chemical imbalance, but in this case there was small-bowel obstruction. The patient was a seventy-five-year-old woman. We gave 1.8 per cent sodium chloride solution, because she had a low chloride, and she went into severe pulmonary edema, which complicated therapy from that point on. Incidentally she also traveled the same path as the patient in the case under discussion. One must be careful about using concentrated saline solution in older people despite the chemical levels.

*Volhard, F., and Fahr, T. *Die Brightsche Nierenkrankheit.* 292 pp. Berlin: Julius Springer, 1914. P. 7.

The New England Journal of Medicine

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The Boston Medical and Surgical Journal

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

FEBRUARY MEETING OF THE COUNCIL

A STATED meeting of the Council of the Massachusetts Medical Society was held at the Boston Medical Library on February 5. Several matters of immediate interest to all members of the Society were discussed and duly acted on.

In the first place, the recommendation of the Committee to Nominate a Director of Medical Information and Education that Dr. John F. Conlin be appointed to this position was unanimously adopted. Dr. Conlin, who is thirty-eight years old, spent from 1926 to 1932 in a monastic order; he graduated from Boston College in 1934 and from Tufts College Medical School in 1938. After an internship at St. Elizabeth's Hospital and a residency at John Adams Hospital in Chelsea, he entered the Army in 1942 and was discharged with the rank of colonel in 1946. During the last session of the Legislature he was extremely helpful in the fight against the Anti-Vivisection Bill. All in all, it appeared to the members of the committee that Dr. Conlin was highly qualified, by training, experience and attainment, for the new position, and the Council concurred. He is now attending courses at the Harvard School of Public Health and will assume office on or about July 1.

The second matter of importance concerned a recommendation by the Committee on Public Health that aggressive support be given to Commissioner Getting's program for improving conditions in state and local public-health departments. His proposals included higher salary levels for the professional personnel, the institution of a sanitary code, the subsidization of local health departments that meet established standards and the promotion of town unions of sufficient size to ensure support of modern public-health programs. The acceptance of this recommendation had not been approved by the Executive Committee of the Council, apparently because it was thought that the Society had no right to recommend salary increases for a particular group of physicians, and several councilors spoke in the same general vein. The discussion was concluded by Dr. Getting, who clearly outlined the difficulties that state and local health departments were encountering because of the inadequate salaries paid to professional workers and predicted a marked deterioration of such services unless something were done in the immediate future. He added that this directly concerned the health of the people of the Commonwealth, and that because of this, his program should be supported by the Society. The recommendation was approved by the Council with only a few dissenting votes.

Finally, the report of the Committee to Study Increase in Assessment of Dues was presented. It was brought out that the activities of the Society had greatly increased in recent years and that the sum needed to pay full-time and part-time salaries had proportionately grown. Attention was called to the need for a permanent headquarters for the Society, for some fund to aid the widows and children of deceased physicians, for one to help financially physicians who are incapacitated by

chronic illness or other cause and for the establishment of a retirement fund for the full-time employees of the Society. Furthermore, the report recognized the need of the Boston Medical Library for financial assistance and expressed the opinion that the library is an asset of the Society that should not be lost. In view of these facts, the committee recommended that the annual dues be increased to $20.00, with the possibility that they might eventually be raised to $25.00. The Executive Committee of the Council had approved the report and had made the following recommendations: that the annual dues for regular members be raised to $25.00; that the rate become effective on January 1, 1948; and that of this sum, $5.00 be earmarked for the Boston Medical Library. After a relatively short discussion, these recommendations, with two minor amendments, were adopted.

MORE PROTEIN FOR PREMATURE INFANTS

THE care of the premature infant constitutes, in pediatric practice, a particular problem by itself, with faithful attention to detail as the usual price of success. Three cardinal principles, with their ramifications, have long been recognized. These are maintenance of a suitable external environment, with special reference to temperature and oxygen content, protection against infection and suitable nourishment.

The necessity for the first two is in every case immediate; the third cannot be long delayed, and its problems are receiving renewed attention with recognition of the possibility that human milk is not necessarily the ideal food for the premature infant, regardless of the value it may have for the full-term infant.

Three Swedish investigators, Jorpes, Magnusson and Wretlind,[1,2] recognizing that the infant born several weeks before term has different nutritional requirements from the full-term newborn infant, have devised a supplementary food consisting of all the essential amino acids. The mixture used, made by the enzymatic hydrolysis of casein with pancreatic ferments, was added to human milk and in every case was followed by considerably greater gains in weight than those that were obtained with human milk alone or when supplemented by unhydrolyzed casein.

Although these reports are among the first on the direct use of the amino acids to improve weight gain of premature infants, other writers have recognized the unusual needs of these patients for extra protein, calcium and phosphorus. Thus, Gordon and Levine,[3] in 1944, stressed the wide variability in the nutritional needs of individual infants, whether breast or artificially fed, and pointed out the relative inability of premature infants to absorb fat, as evidenced by their frequent excessive loss of calories in the form of fecal fat. Not only are they apparently unable to utilize much fat, in which human milk is rich, but also they especially need protein, calcium and phosphorus, in which human milk is relatively low.

The implication is obvious: human milk, designed by Nature as a suitable food for the average full-term infant, must not be dogmatically and doggedly urged as the ideal food for all infants. Otherwise its employment needs no such unusual defense or apology as was offered by the medical student who, when required in an examination to state three particulars in which human milk is superior to cow's milk, wrote that it is cleaner, that it is more digestible and that it comes in more attractive containers.

REFERENCES

1. Jorpes, J. E. Magnusson, J. H., and Wretlind, A. Casein hydrolysate for premature infants. *Lancet* 2:228-232, 1946.
2. Magnusson, J. H. Use of amino acid mixture (casein-hydrolysate) as supplementary feeding for prematures during first weeks of life. *Acta paediat.* 32:599-625, 1945.
3. Gordon, H. H., and Levine, S. Z. Metabolic basis for individualized feeding of infants, premature and full-term. *J. Pediat.* 25:464-475, 1944.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

BACTERIOLOGICAL LABORATORY MOVES

The Bacteriological Laboratory of the Massachusetts Department of Public Health has been moved from the State House and is now established in its new quarters at the old Bussey Institute building near the Arnold Arboretum. All requests for bacteriologic outfits and all specimens should be addressed to the State Diagnostic Laboratory, 281 South Street, Jamaica Plain 30. The telephone is ARNold 5440.

OFFICIAL OPENING OF NEW BLOOD PROCESSING LABORATORY

The Division of Biologic Laboratories of the Massachusetts Department of Public Health will have open house on March 26 in conjunction with

the formal dedication of the Blood Processing Laboratory at 375 South Street, Jamaica Plain.

Official opening of the Blood Processing Laboratory, the first state-operated laboratory designed specifically for large-scale blood processing and fractionation, will give physicians and others an opportunity to see in operation the equipment, methods and technics involved in mass production of blood derivatives. Staff doctors and technicians will be at hand to explain the work and to furnish any pertinent information desired by visitors. Glass-paneled refrigeration, sterilizing and filling rooms make it possible for onlookers to observe each part of the processing without the necessity of entering these rooms.

Although the occasion is primarily for the dedication of the new laboratory, the Antitoxin and Vaccine Laboratory will also be open to accommodate those who are interested in the preparation of the serums, vaccines and antitoxins that are manufactured there for distribution throughout the Commonwealth.

Open house will be held during the morning from 9:00 to 12:00, and in the evening from 6:00 to 9:00. Conducted group tours will be part of the activities of the day.

A cordial invitation to visit the laboratories is extended to all.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Nitrous Oxide-Oxygen Anesthesia: McKesson–Clement viewpoint and technique. By Major F. W. Clement, M.C., A.U.S., anesthetist to Toledo, Mercy and St. Vincent's hospitals, Toledo, Ohio. Second edition, thoroughly revised. 8°, cloth, 288 pp., with 92 illustrations. Philadelphia: Lea and Febiger, 1945. $4.50.

This new edition has been revised in the light of knowledge gained during World War II. During the period there have been no radical changes in either the agents used for anesthesia or their methods of administration, but much has been learned of the physiology of lowered oxygen tensions encountered in aviation. In this revised edition the changes are those of details rather than alterations of the original text. Changes and additions include the commonly accepted theory of nitrous oxide-oxygen anesthesia, with greater detail of its method of administration, the possible dangers associated with prolonged oxygen deficiency, the mechanism and treatment of shock, the role of carbon dioxide and of the sino-aortic areas and the compensatory reflex mechanism that protects the body in the presence of lower oxygen intake. The chapter on dental anesthesia has been enlarged to include more details on the use of the nasal-pharyngeal airway. This is a comprehensive monograph on its subject.

New Goals for Old Age. Edited by George Lawton. 8°, cloth, 210 pp. Second printing. New York: Columbia University Press, 1945. $2.75.

This composite work brings together the various social and medical aspects of old age. The material was originally delivered as lectures in a course on mental health and old age, under the Section on the Care of the Aged of the Welfare Council of New York City, during 1940–1941. The lectures are here brought together for the first time. An interesting final chapter is contributed by an aged woman who spent some of the happiest years of her life in a home for the aged. She is nearly eighty years old and entitles the chapter, "How it feels to be seventy-five and a woman." A bibliography of fifteen pages is appended to the text.

Bacillary Dysentery, Colitis and Enteritis. By Joseph Felsen, M.D., director of medical research, Bronx Hospital, New York, and director, International and Pan-American Dysentery Registry. 12°, cloth, 618 pp., with 145 illustrations. Philadelphia: W. B. Saunders Company, 1945. $6.00.

This monograph presents a correlated study of the historical, epidemiologic, clinical, pathological, bacteriologic, serologic and therapeutic aspects of bacillary dysentery. Dr. Felsen is an authority on the subject, having dealt with epidemics, as well as clinical cases in their various manifestations. He established the International Dysentery Register as a means of promoting co-ordinated study and preventive activity. He divides his subject into two main sections dealing with the acute and chronic forms of the disease and including chronic ulcerative colitis and chronic distal ileitis. An appendix is devoted to the technical methods used in the diagnosis of the disease. The last part of this chapter considers the prevention and control of bacillary dysentery and other infectious diarrheas. This is the first comprehensive study on the subject published in the United States. An extensive bibliography of ninety-six pages is appended to the text. This monograph should be in all medical libraries and in the libraries of physicians interested in the disease.

NOTICES

ANNOUNCEMENT

Dr. Armand M. Gamboa announces the removal of his office to 475 Commonwealth Avenue, Boston.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the Sheltered Workshop of the Boston Tuberculosis Association, 35 Tyler Street, Boston, on Tuesday, March 18, at twelve noon. Dr. John Homans will speak on "Arterial Deficiencies in the Legs in Middle and Advanced Age."

Physicians are cordially invited to attend.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The oral and written examinations for fellowship in the American College of Chest Physicians will be held at Atlantic City on June 5. Applicants for fellowship in the College who plan to take these examinations should communicate at once with the Executive Secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10.

The thirteenth annual meeting of the College is scheduled to be held at the Ambassador Hotel, Atlantic City, June 5 to 8. The convocation for new fellows and life members of the college will be held on the first day of the meeting, when certificates will be awarded to fellows and life members admitted since June, 1946.

PRIZE CONTEST

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons recently announced that the annual prize contest will be conducted again this year. Requests for detailed information should be addressed to the secretary, Dr. James R. Bloss, 418 Eleventh Street, Huntington 1, West Virginia.

(*Notices continued on page xix*)

NOTICES (*Continued from page 418*)

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, March 20

Friday, March 21

*9:00-10:00 a.m. Radioactive Iodine in Hyperthyroidism. Dr. Earle M. Chapman. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, March 24

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, March 25

*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

Wednesday, March 26

*9:00-10:00 a.m. The History of the Concept of Functional Nervous Disease. Dr. A. Warren Stearns. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m.-12:00 m. Medical Clinic. Amphitheater, Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*7:15 p.m. Graduate Seminar in Pediatrics. Children's Medical Service, Amphitheater 3A, Massachusetts General Hospital.

*Open to the medical profession.

October 11-May 14. Metropolitan State Hospital. Page 398, issue of September 12.

March 18. South End Medical Club. Page 418.

March 20. Food and Health Conference. Page 340, issue of February 27.

March 25. Boston City Hospital House Officers' Association. Page 382, issue of March 6.

March 26. Tufts Medical Alumni Association. Page 382, issue of March 6.

March 27. Winthrop Community Hospital. Page 340, issue of February 27.

March 28 and 29. American College of Surgeons. Page 382, issue of March 6.

April 8. Harvard Medical Society. Amphitheater, Peter Bent Hospital. 8:00 p.m.

April 10. Physiotherapy, Its Practical Application and Its Limitations. Dr. Franklin P. Lowry. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 15-18. Postgraduate Institute. Page 382, issue of March 6.

April 28-May 2. American College of Physicians. Page 206, issue of August 8.

May 20-22. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

May 20-22. Massachusetts Physicians' Art Association. Page 340, issue of February 27.

June 5-8. American College of Chest Physicians. Page 418.

June 7 and 8. American Society for the Study of Sterility. Page 304, issue of February 20.

June 9-13. American Medical Association. Page 698, issue of November 7.

June 16-18. New England Health Institute. Page 340, issue of February 27.

June 30-July 3. American Urological Association. Hotel Statler, Buffalo.

September 2-7. International Cancer Research Congress. Page 340, issue of February 27.

September 8-12. Third American Congress on Obstetrics and Gynecology. Page 340, issue of February 27.

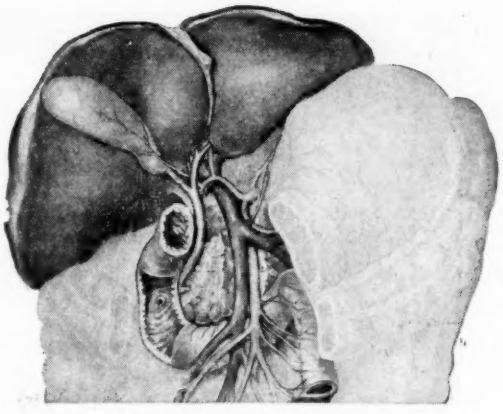
District Medical Society

PLYMOUTH

March 20. Goddard Hospital, Brockton.

April 17. State Farm, Bridgewater.

May 15. Lakeville Sanatorium, Lakeville.



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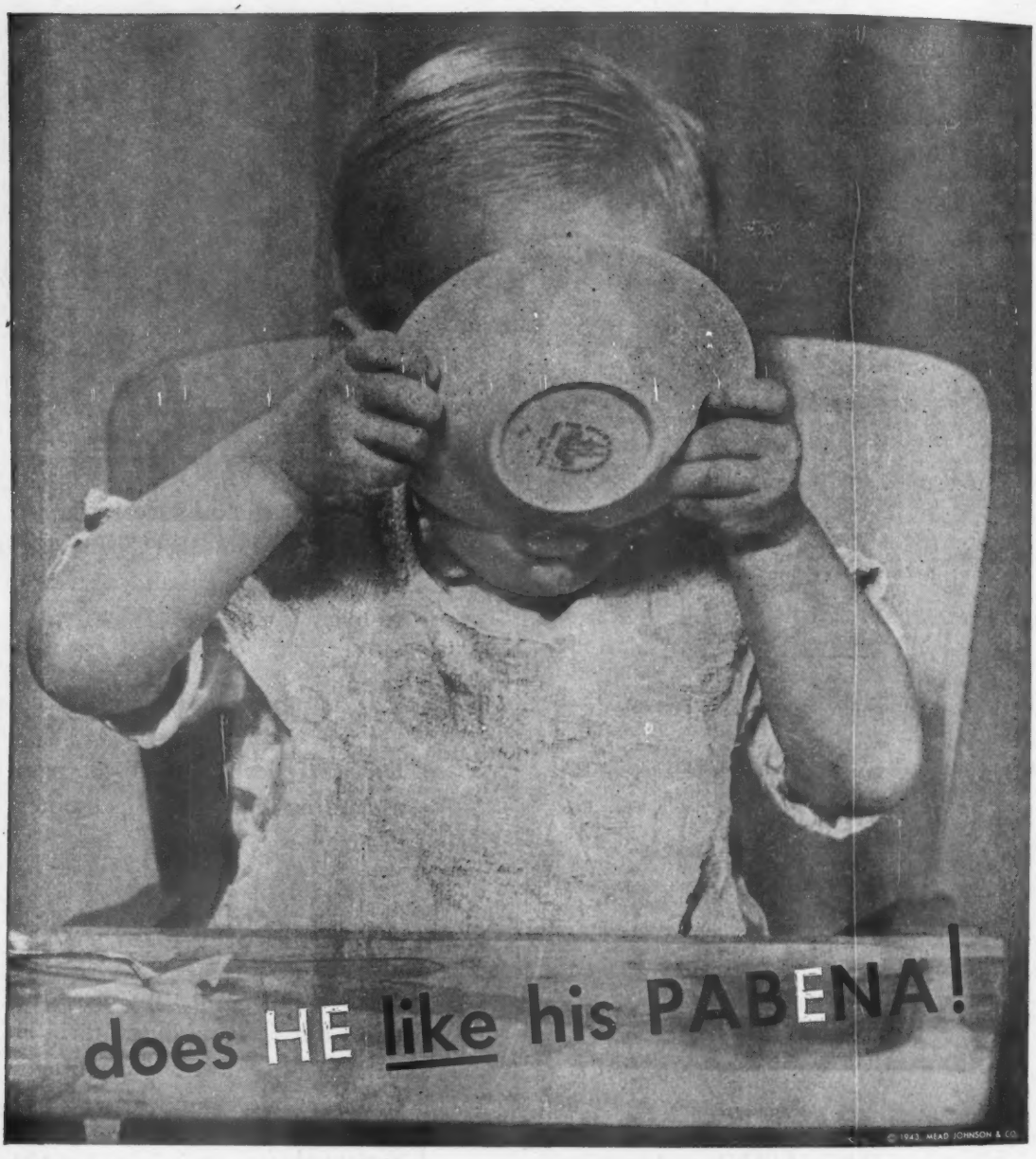

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